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NEWS 4	DEC 14	2006 MeSH terms loaded in MEDLINE/LMEDLINE
NEWS 5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
NEWS 6	DEC 14	CA/CAplus to be enhanced with updated IPC codes
NEWS 7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 13	JAN 30	Saved answer limit increased
NEWS 14	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 15	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 16	FEB 22	Status of current WO (PCT) information on STN
NEWS 17	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 18	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 19	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 20	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 21	FEB 28	TOXCENTER reloaded with enhancements
NEWS 22	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 23	MAR 01	INSPEC reloaded and enhanced
NEWS 24	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 25	MAR 08	X.25 communication option no longer available after June 2006

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:32:13 ON 16 MAR 2006

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:32:24 ON 16 MAR 2006
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 MAR 2006 HIGHEST RN 876856-38-1
DICTIONARY FILE UPDATES: 14 MAR 2006 HIGHEST RN 876856-38-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

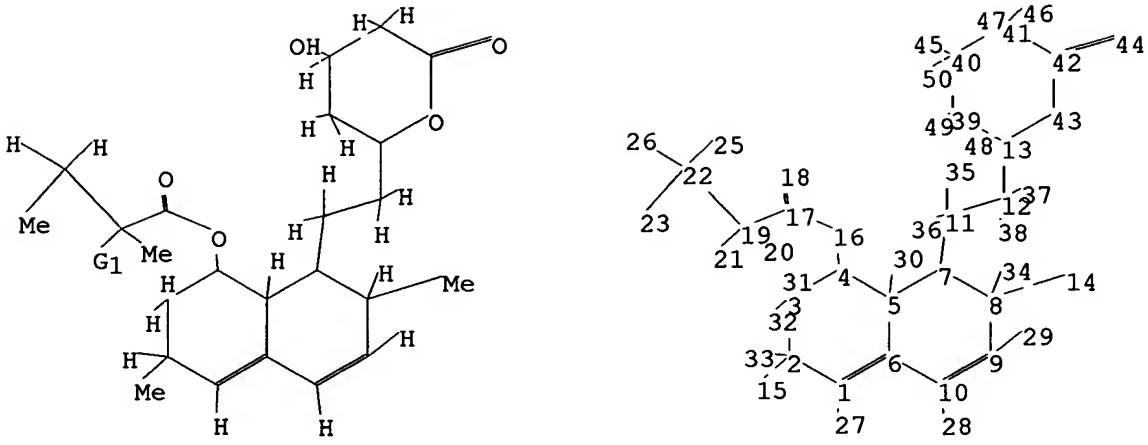
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10539736a.str



chain nodes :
11 12 14 15 16 17 18 19 20 21 22 23 25 26 27 28 29 30 31 32 33
34 35 36 37 38 44 45 46 47 48 49 50
ring nodes :
1 2 3 4 5 6 7 8 9 10 13 39 40 41 42 43
chain bonds :
1-27 2-15 2-33 3-31 3-32 4-16 5-30 7-11 8-14 8-34 9-29 10-28 11-12
11-35 11-36 12-13 12-37 12-38 16-17 17-18 17-19 19-20 19-21 19-22 22-23
22-25 22-26 39-48 39-49 40-45 40-50 41-46 41-47 42-44
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 13-39 13-43 39-40 40-41
41-42 42-43
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 4-16 5-6 5-7 6-10 7-8 8-9 9-10 13-39 13-43 16-17
17-18 19-21 39-40 40-41 40-45 41-42 42-43 42-44
exact bonds :
1-27 2-15 2-33 3-31 3-32 5-30 7-11 8-14 8-34 9-29 10-28 11-12 11-35
11-36 12-13 12-37 12-38 17-19 19-20 19-22 22-23 22-25 22-26 39-48 39-49
40-50 41-46 41-47

G1:H,CH3

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:CLASS 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS
36:CLASS 37:CLASS 38:CLASS 39:Atom 40:Atom 41:Atom 42:Atom 43:Atom 44:CLASS
45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS 50:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
'1L ' IS NOT A VALID STRUCTURE FORMAT KEYWORD
Structure Formats
SIA ----- Structure Image, Attributes, and map table if it contains
data. (Default)
SIM ----- Structure IMage.
SAT ----- Structure ATtributes and map table if it contains data.
SCT ----- Structure Connection Table and map table if it contains

```
          data.
SDA ----- All Structure DAta (image, attributes, connection table and
          map table if it contains data).
NOS ----- NO Structure data.
ENTER STRUCTURE FORMAT (SIM), NOS:n
'N' IS NOT A VALID STRUCTURE FORMAT KEYWORD
Structure Formats
SIA ----- Structure Image, Attributes, and map table if it contains
          data.  (Default)
SIM ----- Structure IMage.
SAT ----- Structure ATtributes and map table if it contains data.
SCT ----- Structure Connection Table and map table if it contains
          data.
SDA ----- All Structure DAta (image, attributes, connection table and
          map table if it contains data).
NOS ----- NO Structure data.
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L1              STR


=> d l1
L1 HAS NO ANSWERS
L1              STR
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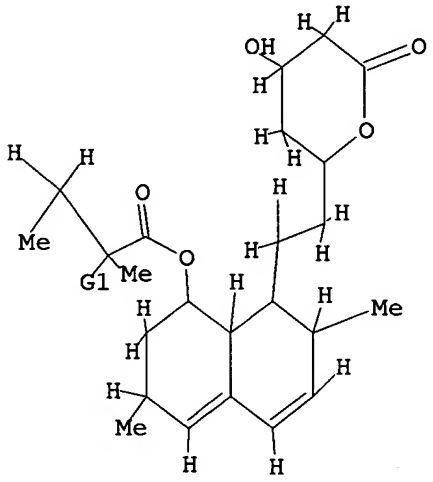


```
G1 H,Me


Structure attributes must be viewed using STN Express query preparation.


=> s l1
SAMPLE SEARCH INITIATED 09:33:24 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      100 TO ITERATE

100.0% PROCESSED      100 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          1401 TO     2599
PROJECTED ANSWERS:                3 TO      163

L2            3 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 09:33:29 FILE 'REGISTRY'
```

FULL SCREEN SEARCH COMPLETED - 2081 TO ITERATE

100.0% PROCESSED 2081 ITERATIONS 62 ANSWERS
SEARCH TIME: 00.00.01

L3 62 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 167.38 167.59

FILE 'CAPLUS' ENTERED AT 09:33:36 ON 16 MAR 2006
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FILE COVERS 1907 - 16 Mar 2006 VOL 144 ISS 12
FILE LAST UPDATED: 15 Mar 2006 (20060315/ED)

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=> s l3 full
L4 4635 L3

=> s l4 and py<2004
23839623 PY<2004
L5 3408 L4 AND PY<2004

=> s l5 and hydrolyz?
227583 HYDROLYZ?
L6 31 L5 AND HYDROLYZ?

=> s l4 and hydrolyz?
227583 HYDROLYZ?
L7 42 L4 AND HYDROLYZ?

=> s l7 and lacton?
72790 LACTON?
L8 14 L7 AND LACTON?

=> d ibib abs hitstr 1-14

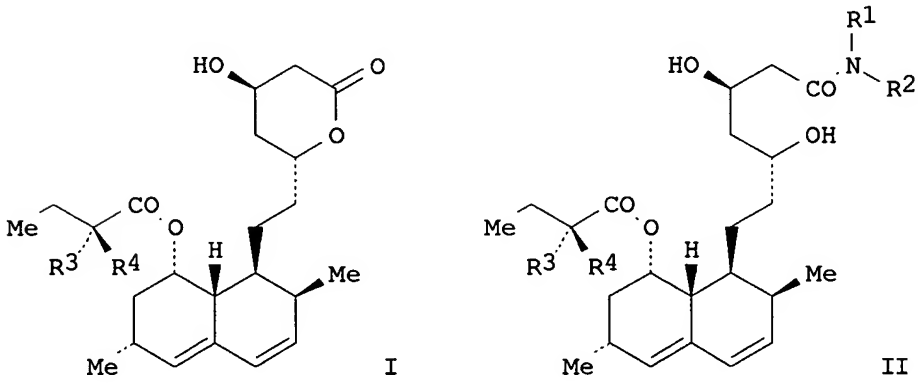
L8 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:638861 CAPLUS
DOCUMENT NUMBER: 143:133225
TITLE: A novel process for the preparation of simvastatin
INVENTOR(S): Parthasaradhi Reddy, Bandi; Rathnakar Reddy, Kura; Raji Reddy, Rapolu; Muralidhara Reddy, Dasari; Subash

Chander Reddy, Kesireddy
PATENT ASSIGNEE(S): Hetero Drugs Limited, India
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005066150	A1	20050721	WO 2004-IN3	20040102

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2004-IN3 20040102
OTHER SOURCE(S): CASREACT 143:133225; MARPAT 143:133225
GI



AB A process for manufacturing simvastatin I (R3 = R4 = Me) was disclosed and comprised the preparation of amide intermediates II [R1 = alkyloxyalkyl, alkylthioalkyl, alkoxyarylalkyl, alkylthioarylalkyl, alkoxycycloalkyl, alkylthiocycloalkyl, etc.] and a subsequent methylation/**lactonization** reaction sequence. Thus, lovastatin I (R3 = H, R4 = Me) was reacted with methoxyethylamine to give amide II [R1 = H, R2 = (CH2)2OMe, R3 = H, R4 = Me] which was subsequently alpha methylated on 2-methylbutyryl side chain to form II [R1 = H, R2 = (CH2)2OMe, R3 = R4 = Me] which was in turn **hydrolyzed** and **lactonized** to produce simvastatin of high purity.

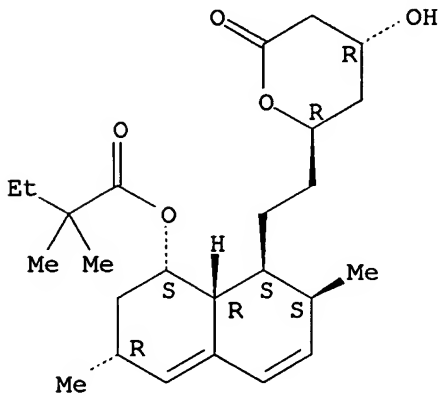
IT **79902-63-9P**, Simvastatin
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of simvastatin)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-

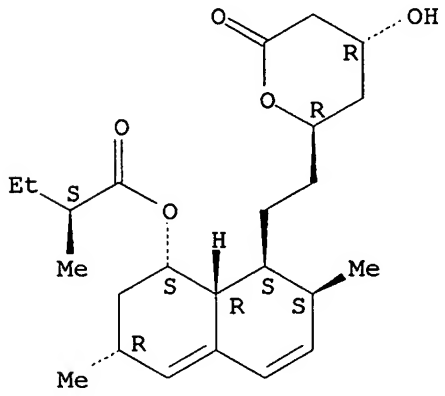
naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **75330-75-5**, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of simvastatin)
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:524462 CAPLUS
DOCUMENT NUMBER: 144:186918
TITLE: Human paraoxonases (PON1, PON2, and PON3) are **lactonases** with overlapping and distinct substrate specificities
AUTHOR(S): Draganov, Dragomir I.; Teiber, John F.; Speelman, Audrey; Osawa, Yoichi; Sunahara, Roger; La Du, Bert N.
CORPORATE SOURCE: Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI, 48109, USA
SOURCE: Journal of Lipid Research (2005), 46(6), 1239-1247
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: American Society for Biochemistry and Molecular Biology, Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English

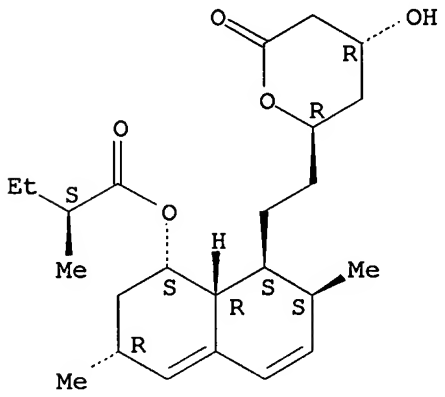
AB The paraoxonase (PON) gene family in humans has three members, PON1, PON2, and PON3. Their physiol. role(s) and natural substrates are uncertain. We developed a baculovirus-mediated expression system, suitable for all three human PONs, and optimized procedures for their purification The recombinant PONs are glycosylated with high-mannose-type sugars, which are important for protein stability but are not essential for their enzymic activities. Enzymic characterization of the purified PONs has revealed them to be **lactonases/lactonizing** enzymes, with some overlapping substrates (e.g., aromatic **lactones**), but also to have distinctive substrate specificities. All three PONs metabolized very efficiently 5-hydroxy-eicosatetraenoic acid 1,5-**lactone** and 4-hydroxy-docosahexaenoic acid, which are products of both enzymic and nonenzymic oxidation of arachidonic acid and docosahexaenoic acid, resp., and may represent the PONs' endogenous substrates. Organophosphates are **hydrolyzed** almost exclusively by PON1, whereas bulky drug substrates such as lovastatin and spironolactone are **hydrolyzed** only by PON3. Of special interest is the ability of the human PONs, especially PON2, to **hydrolyze** and thereby inactivate N-acyl-homoserine **lactones**, which are quorum-sensing signals of pathogenic bacteria. None of the recombinant PONs protected low d. lipoprotein against copper-induced oxidation in vitro.

IT **75330-75-5**, Lovastatin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human paraoxonases PON1, PON2, and PON3 isoenzymes are **lactonases** with overlapping and distinct substrate specificities)

RN 75330-75-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:423744 CAPLUS
DOCUMENT NUMBER: 142:469285
TITLE: Pharmaceutical formulations comprising simvastatin, a solvent and a surfactant and methods of making same
INVENTOR(S): Flashner-Barak, Moshe; Lerner, Itzhak E.; Rosenberger, Vered; Moldavski, Naomi
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044258	A1	20050519	WO 2004-US36931	20041105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005192340	A1	20050901	US 2004-981953	20041105

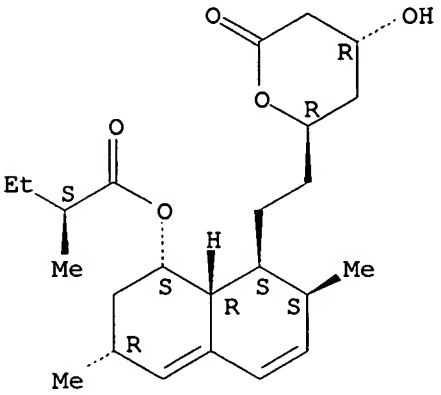
PRIORITY APPLN. INFO.: US 2003-517650P P 20031105

AB The invention encompasses a compns. of at least one statin, at least one pharmaceutically acceptable solvent, and at least one surface active agent. In the composition, about 9% to about 50% by weight of the statin is **hydrolyzed** from a closed **lactone** form to an open hydroxy acid form when the composition is placed in an aqueous acidic solution The invention also encompasses method of making the composition and methods of treating high cholesterol, multiple sclerosis, and/or Alzheimer's disease using the compns. described herein.

IT **75330-75-5**, Lovastatin **79902-63-9**, Simvastatin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulations comprising simvastatin, solvent and surfactant and methods of making same)

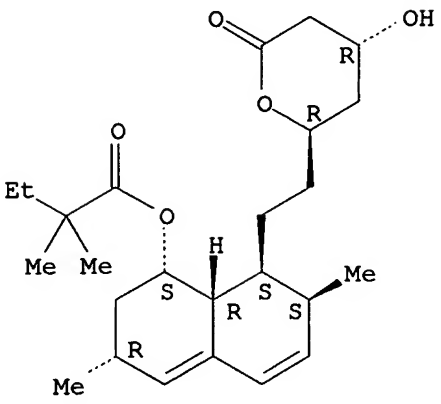
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:915169 CAPLUS
DOCUMENT NUMBER: 142:113813
TITLE: Improved method for manufacturing Simvastatin as hyperlipidemia therapeutic agent
INVENTOR(S): Jung, Yong Jun; Kim, Sang Ho; Lee, Tae Rim
PATENT ASSIGNEE(S): Kolon Ind. Inc., S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2002017162	A	20020307	KR 2000-50321	20000829

PRIORITY APPLN. INFO.: KR 2000-50321 20000829

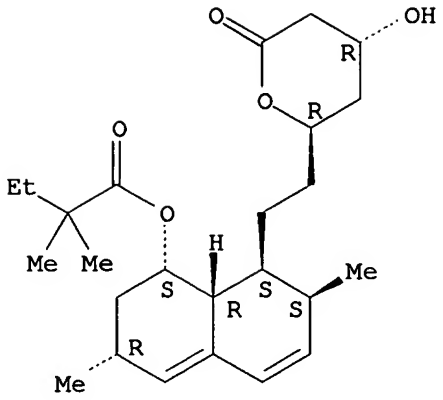
AB Provided is an improved manufacturing method of Simvastatin, which is a hyperlipidemia therapeutic agent and represented by the formula(1), by using a compound of the formula(2) as a starting material. The manufacturing method comprises the steps of: **hydrolyzing** the **lactone** ring of lovastatin of the formula(2) with pyrrolidine or piperidine to obtain a compound of the formula(3); protecting two hydroxy groups to obtain acetonide compound of the formula(4); producing enolate by using Bu lithium and pyrrolidine from the compound of the formula(4) then methylating it with methyliodine to obtain a compound of the formula(5); removing a protection group from the acetonide with hydrochloride solution to obtain a compound of the formula(6); and **hydrolyzing** an amide compound with sodium hydroxide then forming a **lactone** ring with hydrochloride solution to obtain Simvastatin of the formula(1).

IT **79902-63-9P**, Simvastatin
RL: IMF (Industrial manufacture); PREP (Preparation)
(method for manufacturing Simvastatin as hyperlipidemia therapeutic agent)

RN 79902-63-9 CAPLUS

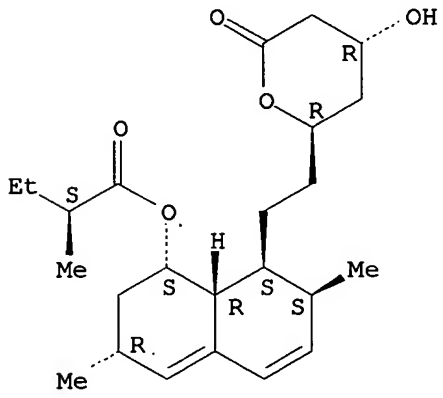
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **75330-75-5**, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for manufacturing Simvastatin as hyperlipidemia therapeutic agent)
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



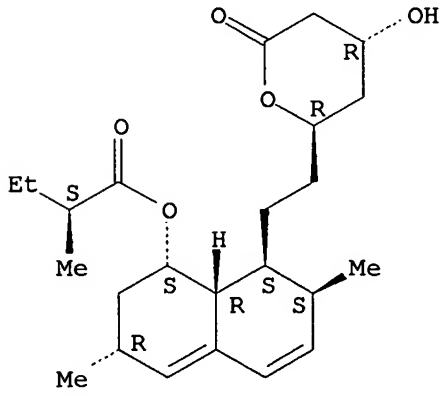
L8 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:704323 CAPLUS
DOCUMENT NUMBER: 140:107335
TITLE: **Lactonase** and **lactonizing** activities of human serum paraoxonase (PON1) and rabbit serum PON3
AUTHOR(S): Teiber, John F.; Draganov, Dragomir I.; La Du, Bert N.
CORPORATE SOURCE: Department of Pharmacology, Medical School, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Biochemical Pharmacology (2003), 66(6), 887-896
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human paraoxonase (PON1) was previously shown to **hydrolyze** over 30 different **lactones** (cyclic esters). In the present study purified human PON1 was found to catalyze the reverse reaction (**lactonization**) of a broad range of hydroxy acids. Hydroxy acid **lactonization** or **lactone** hydrolysis is catalyzed until equilibrium between the open and closed forms is reached.

Lactonization by PON1 was calcium-dependent, had a pH optimum of 5.5-6 and could be stimulated with dilauroylphosphatidylcholine. Rabbit serum PON3 and a serine esterase in mouse plasma, presumably a carboxylesterase, also catalyzed hydroxy acid **lactonization**. Two endogenous oxidized unsatd. fatty acids, (±)4-hydroxy-5E,7Z,10Z,13Z,16Z,19Z-docosahexaenoic acid (4-HDoHE) and (±)5-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid (5-HETE) **lactone**, were very efficiently **lactonized** and **hydrolyzed**, resp., by PON1. Human and mouse plasma samples also catalyzed 4-HDoHE **lactonization** and 5-HETE **lactone** hydrolysis. Studies with the PON1 inhibitor EDTA and the serine esterase inhibitor phenylmethylsulfonylfluoride suggest that about 80-95% of both activities can be attributed to PON1 in the human samples. In the mouse sample, PON1 accounted for about 30% of the 4-HDoHE **lactonizing** activity and 72% of the 5-HETE **lactonase** activity. Our results demonstrate that PON1 can **lactonize** the hydroxy acid form of its **lactone** substrates and that reversible hydrolysis of **lactones** may be a property of **lactonases** that is not generally considered. Also, the high activity of PON1 towards 4-HDoHE and 5-HETE **lactone** suggests that oxidized eicosanoids and docosanoids may be important physiol. substrates for PON1.

IT **75330-75-5**, Lovastatin **79902-63-9**, Simvastatin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**lactonase** and **lactonizing** activities of human serum paraoxonase PON1 and rabbit serum PON3)

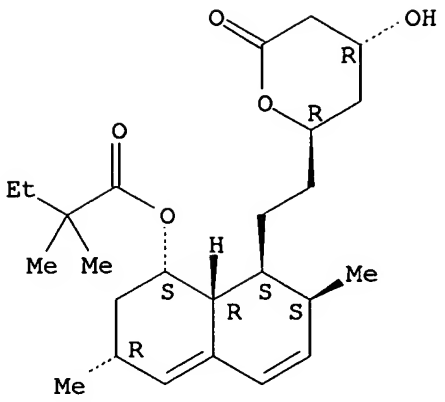
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:830276 CAPLUS
DOCUMENT NUMBER: 137:326808
TITLE: Method for alkylating the alpha carbon of the 2-methylbutyrate secondary chain of lovastatin
INVENTOR(S): Galeazzi, Edvige; Garcia, Gustavo A.; Lara, Fernando; Lopez, Gema; Martinez, Orestes; Tisselli, Eugenio; Trejo, Alicia
PATENT ASSIGNEE(S): Fermic S.A. de C.V., Mex.
SOURCE: U.S., 10 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6472542	B1	20021029	US 2001-996664	20011129
WO 2003045935	A1	20030605	WO 2002-IB4082	20020906
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002341268	A1	20030610	AU 2002-341268	20020906
PRIORITY APPLN. INFO.:			US 2001-996664 A	20011129
			WO 2002-IB4082 W	20020906

AB Simvastatin, which is a very active anti-hypercholesterolemic agent, is produced from lovastatin in high yield and in pharmaceutical purity by forming an amide of lovastatin and protecting the free hydroxyl groups of the lovastatin amide with hexamethyldisilazane (HMDS) to form a protected lovastatin amide. The α-carbon of the 2-methylbutyrate secondary chain of the protected lovastatin amide may be methylated to form a protected simvastatin amide. The protecting groups may be removed therefrom by quenching the methylation reaction with water. The simvastatin amide which is obtained may be **hydrolyzed** to form simvastatin acid, followed by forming a simvastatin ammonium salt,

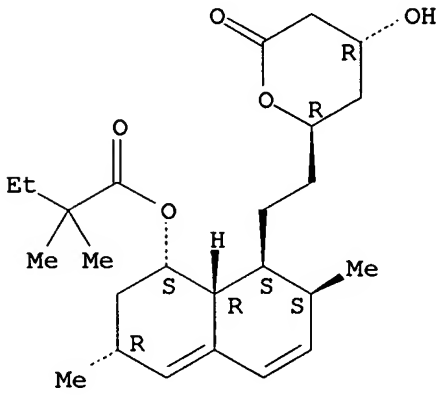
lactonizing the salt to form simvastatin, and recrystg. the thus formed crude Simvastatin to a high degree of purity. The HMDS protecting agent for the **lactone** hydroxyl groups of Lovastatin is selected so as to result in a reaction that does not produce acid so that a base, such as imidazole, is not required to neutralize the acidity of the reaction medium. Another advantage of using HMDS as a protecting agent is that the removal of the protecting agent after the methylation reaction is carried out simply, for example, by water quenching. The **lactonization** reaction of the present invention may be carried out using a low b.p. solvent, such as methylene chloride, in the presence of inorg. acids such as sulfuric, hydrochloric, methanesulfonic or phosphoric acid as catalyst.

IT **79902-63-9P**
RL: IMF (Industrial manufacture); PREP (Preparation)
(method for alkylating the alpha carbon of 2-methylbutyrate secondary chain of lovastatin)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

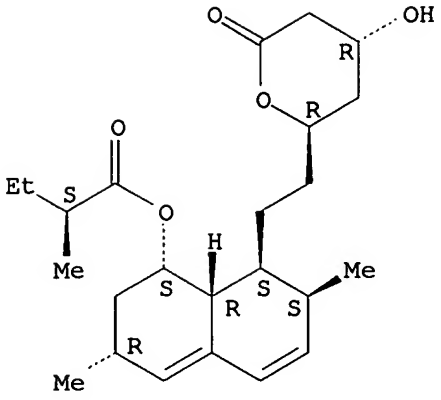


IT **75330-75-5**, Lovastatin
RL: RCT (Reactant); RACT (Reactant or reagent)
(method for alkylating the alpha carbon of 2-methylbutyrate secondary chain of lovastatin)

RN 75330-75-5 CAPLUS

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:868660 CAPLUS
DOCUMENT NUMBER: 136:17261
TITLE: Use of rabbit serum paraoxonase 3 (PON3), a high density lipoprotein-associated **lactonase** that protects low density lipoprotein against oxidation, in therapy
INVENTOR(S): La Du, Bert N.; Draganov, Dragomir I.; Stetson, Philip; Watson, Catherine E.
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001090336	A2	20011129	WO 2001-US16126	20010518
WO 2001090336	A3	20021003		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6573370	B1	20030603	US 2000-574377	20000519
US 2003144228	A1	20030731	US 2002-184194	20020627
US 6916472	B2	20050712		

PRIORITY APPLN. INFO.: US 2000-574377 A 20000519

AB The present invention relates to compns. comprising paroxonase 3 genes and polypeptides, in particular to compns. comprising rabbit PON3 genes and polypeptides. The present invention also provides methods for using PON3 genes and peptides in the treatment of endotoxemia, oxidative damage, chemical toxicity, and other conditions. In some embodiments, the present invention provides novel nucleic acid sequences of the rabbit Pon3 gene. In other embodiments, the present invention provides mutants, variants, homologs, chimeras, and fusions of rabbit Pon3. In some embodiments, the present invention provides methods of generating such sequences. In

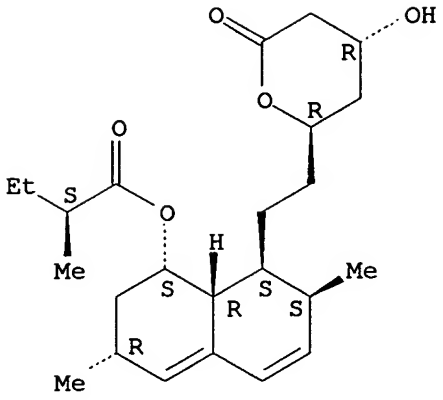
addnl. embodiments, the present invention provides methods of cloning, expressing, purifying, and assaying the biochem. activity of wild type as well as mutants, variants, homologs, chimeras, and fusions of Pon3. In preferred embodiments of the present invention, the present invention provides biol. active rabbit PON3 polypeptides or polypeptide fragments. In certain embodiments, the polypeptides further comprise non-rabbit PON-3 polypeptide sequences (e.g., a biol. active rabbit PON3 polypeptide is provided as a chimera with a human PON3 polypeptide sequence). The present invention also provides methods comprising providing: a biol. active PON3 polypeptide or polypeptide fragment (e.g., including, but not limited to any of the above peptides), a host, and a delivery system; and administering the biol. active rabbit PON3 polypeptide or fragment to the host using the delivery system. In some embodiments, the host is further treated with other PON polypeptides (e.g., PON-1 and/or PON-2 polypeptides), for example, in a mixture with PON-3. The compns. of the present invention find use in the prevention and treatment of diseases and pathol. conditions related to **lactone** production Therapeutic treatments for sepsis, oxidative damage, and chemical toxicity are provided. The paraoxonase gene family contains at least three members: PON1, PON2, and PON3. The physiol. roles of the corresponding gene products are still uncertain. Until recently, only the serum paraoxonase/arylesterase (PON1) had been purified and characterized. Here we report the purification, cloning, and characterization of rabbit serum PON3. PON3 is a 40-kDa protein associated with the high d. lipoprotein fraction of serum. In contrast to PON1, PON3 has very limited arylesterase and no paraoxonase activities but rapidly **hydrolyzes lactones** such as statin prodrugs (e.g. lovastatin). These differences facilitated the complete separation of PON3 from PON1 during purification PON3 **hydrolyzes** aromatic **lactones** and 5- or 6-member ring **lactones** with aliphatic substituents but not simple **lactones** or those with polar substituents. We cloned PON3 from total rabbit liver RNA and expressed it in mammalian 293T/17 cells. The recombinant PON3 has the same apparent mol. mass and substrate specificity as the enzyme purified from serum. Rabbit serum PON3 is more efficient than rabbit PON1 in protecting low d. lipoprotein from copper-induced oxidation This is the first report that identifies a second PON enzyme in mammalian serum and the first to describe an enzymic activity for PON3.

IT **75330-75-5**, Lovastatin **79902-63-9**, Simvastatin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PON3 hydrolysis of; use of rabbit serum paraoxonase 3 (PON3), a high d. lipoprotein-associated **lactonase** that protects low d. lipoprotein against oxidation, in therapy)

RN 75330-75-5 CAPLUS

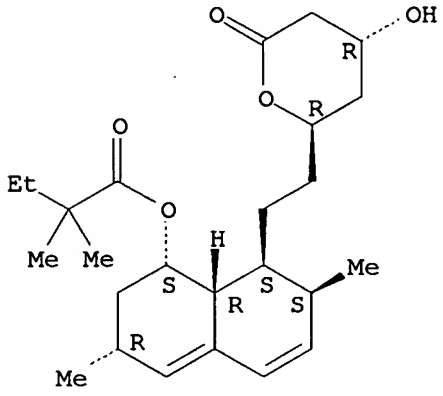
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



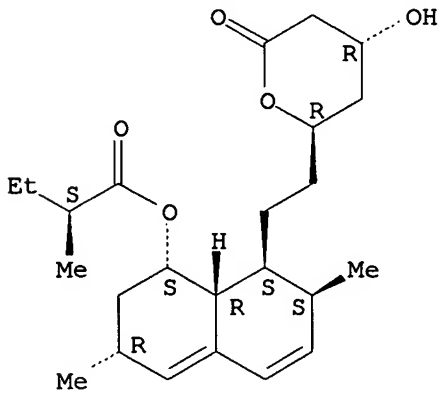
L8 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:757631 CAPLUS
DOCUMENT NUMBER: 134:82617
TITLE: Human serum paraoxonase (PON1) isozymes Q and R **hydrolyze lactones** and cyclic carbonate esters
AUTHOR(S): Billecke, S.; Draganov, D.; Counsell, R.; Stetson, P.; Watson, C.; Hsu, C.; La Du, B. N.
CORPORATE SOURCE: Departments of Anesthesiology and Pharmacology, University of Michigan Medical School, Ann Arbor, MI, 48109-0632, USA
SOURCE: Drug Metabolism and Disposition (2000), 28(11), 1335-1342
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It is well established that human serum paraoxonase (PON1) catalyzes the hydrolysis of organophosphate insecticides and nerve agents, as well as that of a number of aromatic carboxylic acid esters. Our laboratory has recently

found a new class of PON1 substrates that includes at least 30 **lactones** and cyclic carbonate esters. The **lactone** substrates vary in their ring size from 4 to 7 atoms. Substituents on the ring carbons may enhance or reduce the rate of **lactone** hydrolysis. An appreciable degree of stereospecificity exists with some activities differing up to 9-fold between enantiomers (i.e., S-α-hydroxy-γ-butyrolactone is **hydrolyzed** 5 to 9 times faster than the R form). Thiolactones are **hydrolyzed** less efficiently, and some lactams are potent inhibitors. Four **lactone** -containing drugs - spironolactone, mevastatin, simvastatin, and lovastatin - have been identified as substrates for PON1. All **lactone** substrates are **hydrolyzed** by both the Q and R isoenzymes of human serum PON1. However, some **lactone** substrates are **hydrolyzed** faster by the Q than R isoenzyme, whereas others show a reverse preference. Moreover, these new substrates include mogentisic acid **lactone**, mevalonic acid **lactone**, homocysteine thiolactone, and γ-hydroxybutyric acid **lactone** - all **lactone** forms of endogenous compds. It is reasonable to expect that further investigations may uncover PON1 **lactone** substrates that are, themselves, endogenous compds. In this article we characterize the basic enzymic properties of PON1's newly identified hydrolytic activities with **lactone** and cyclic carbonate ester substrates and compare these properties with those of representative arylesters and organophosphates.

IT **75330-75-5**, Lovastatin **79902-63-9**, Simvastatin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(human serum paraoxonase PON1 isoenzymes Q and R **hydrolyze** **lactones** and cyclic carbonate esters)

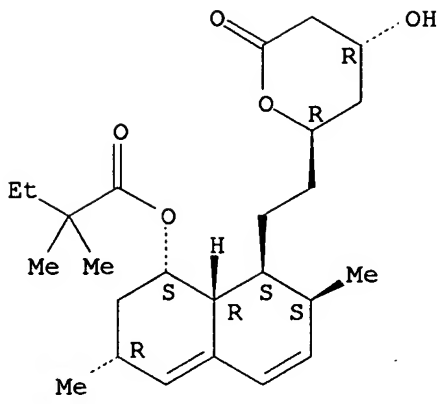
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:756521 CAPLUS
DOCUMENT NUMBER: 133:325641
TITLE: Compositions and methods for increasing the bioavailability of **lactone** ring containing drugs
INVENTOR(S): La Du, Bert N.; Billecke, Scott S.; Counsel, Raymond
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000062775	A1	20001026	WO 2000-US9989	20000414

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

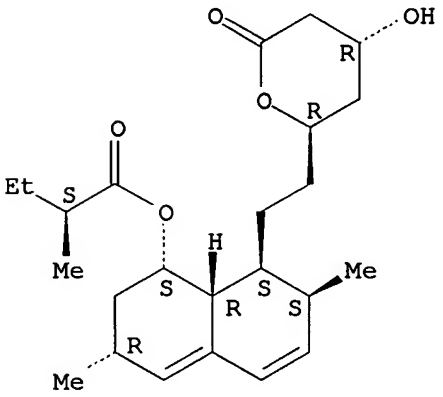
PRIORITY APPLN. INFO.: US 1999-130051P P 19990419

AB Compns. and methods are described for increasing the bioavailability of drugs, and in particular, drugs and prodrugs containing **lactone** structures which are **hydrolyzed** to open forms (carboxylic acids and alcs.) by serum and tissue paraoxonase. Inhibitors of paraoxonase (e.g., lactams) are co-administered with such drugs, thereby preventing paraoxonase from acting on these **lactone** substrates. Such inhibitors are particularly suitable in conjunction with the administration of lovastatin, simvastatin or mevastatin. It is desirable to administer α-ethyl-α-methyl-γ-butyrolactone or α,α-dimethyl-γ-butyrolactone in conjunction with paraoxonase inhibitors to increase the amount of the above **lactones** in the systemic circulation.

IT **75330-75-5**, Lovastatin **79902-63-9**, Simvastatin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods for increasing bioavailability of **lactone**

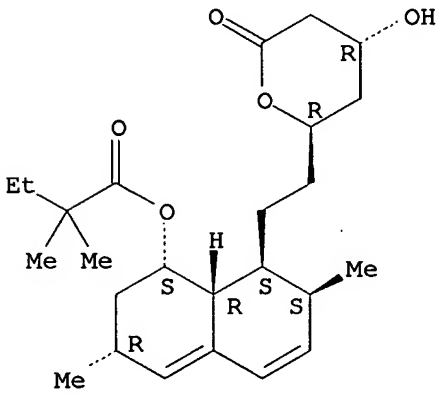
-containing drugs)
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

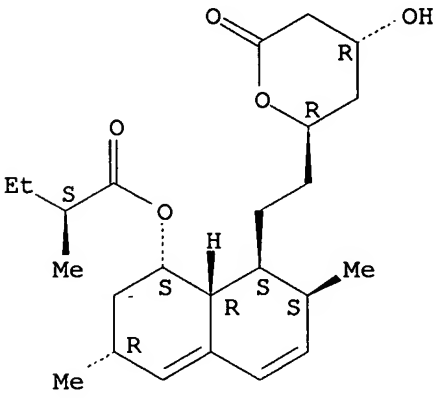


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:731196 CAPLUS
DOCUMENT NUMBER: 132:202648
TITLE: Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
AUTHOR(S): Rogers, John D.; Zhao, Jamie; Liu, Lida; Amin, Raju D.; Gagliano, Kathleen D.; Porras, Arturo G.; Blum, Robert A.; Wilson, Michael F.; Stepanavage, Michael; Vega, Jose M.
CORPORATE SOURCE: Merck Research Labs, West Point, PA, 19486, USA
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis)

(1999), 66(4), 358-366
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This work evaluated the effect of regular-strength grapefruit juice, a cytochrome P 4503A4 inhibitor, on the pharmacokinetics of a commonly prescribed regimen of oral lovastatin. In a randomized crossover study, healthy subjects received a single 40-mg dose of lovastatin in the evening after each had consumed an 8-oz glass of regular-strength grapefruit juice or water with breakfast for 3 consecutive days. The effect of the same grapefruit juice and water regimen on the pharmacokinetics of midazolam (2-mg oral dose given 1 h after the 3rd day of grapefruit juice and water) was used as a pos. control in the same subjects. Inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by plasma was determined by an enzyme inhibition assay, and concns. of lovastatin, lovastatin acid, and midazolam were determined by liquid chromatog.-tandem mass spectrometry. The area under the plasma concentration-time profiles (AUC) and maximum plasma concns. (Cmax) of HMG-CoA reductase-inhibiting substances increased slightly (.apprx.30% for each) after consumption of grapefruit juice. Similar effects on AUC and Cmax (.apprx.40% increase for each) were noted after anal. of plasma which had been **hydrolyzed** (which converts inactive **lactones** to active hydroxy acid species). The AUC and Cmax values for lovastatin approx. doubled in the presence of grapefruit juice, whereas the same parameters for lovastatin acid increased 1.6-fold. Grapefruit juice caused the AUC for midazolam to increase by a factor of .apprx.2.4. Thus, daily consumption of a glass of regular-strength grapefruit juice has a minimal effect on plasma concns. of HMG-CoA reductase inhibitors (.apprx.30%-40% increase) after a 40-mg evening dose of lovastatin.
IT **75330-75-5**, Lovastatin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(grapefruit juice effects on lovastatin-derived hydroxymethylglutaryl Co A reductase inhibitors in human plasma)
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

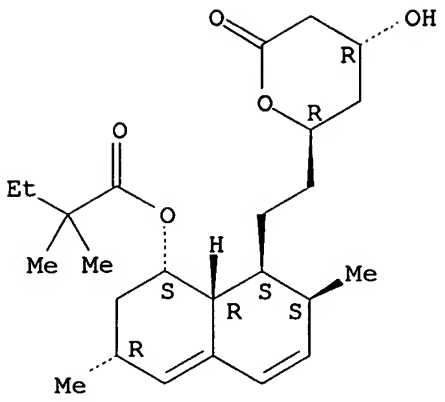
L8 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:466366 CAPLUS
DOCUMENT NUMBER: 127:185251
TITLE: Determination of simvastatin and its active metabolite in human plasma by column-switching high-performance liquid chromatography with fluorescence detection after derivatization with 1-bromoacetylpyrene
AUTHOR(S): Ochiai, Hisao; Uchiyama, Naotaka; Imagaki, Kazuhide; Hata, Shunsuke; Kamei, Toshio
CORPORATE SOURCE: Drug Metab., Dev. Res. Lab., Banyu Pharmaceutical Co., Ltd., Saitama, 360-02, Japan
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1997), 694(1), 211-217
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB By using a fluorescent derivatization and column-switching technique, a highly sensitive and selective high-performance liquid chromatog. (HPLC) method has been developed for the determination of simvastatin (I, β-hydroxy-δ- **lactone** form) and its active **hydrolyzed** metabolite (II, β,δ-dihydroxy acid form of I) in human plasma. A plasma sample spiked with internal stds. was applied to a C8 solid-phase extraction column. I and II were sep. extracted from internal stds. was applied to a C8 solid-phase extraction column. I and II were sep. extracted from plasma into two fractions. I in one of the fractions was **hydrolyzed** to II. A fluorescent derivative was prepared by esterification of II with 1-bromoacetylpyrene in the presence of 18-crown-6 for both fractions. The pyrenacyl ester of II thus obtained was purified on a phenylboronic acid (PBA) solid-phase extraction column, and was measured by column-switching HPLC with fluorescence detection. The calibration curves for both I and II were linear in the concentration range of 0.1-10 ng/mL. The intra-day coeffs. of variation were less than 11.0%, and the accuracies were between 91.7% and 117% within the concentration range for both analytes. The limits of quantification (LOQ) for both analytes were set to 0.1 ng/mL. This assay method has adequate sensitivity and selectivity to measure the concns. of I and II in human plasma from clin. studies.

IT **79902-63-9**, Simvastatin
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(determination of simvastatin and active metabolite in human plasma by column-switching high-performance liquid chromatog. with fluorescence detection after derivatization with bromoacetylpyrene)

RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



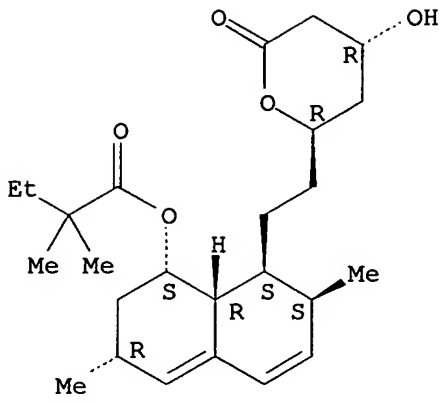
L8 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:240910 CAPLUS
DOCUMENT NUMBER: 126:327221
TITLE: Purification and characterization of a lovastatin esterase from Clonostachys compactiuscula
AUTHOR(S): Schimmel, Timothy G.; Borneman, W. Scott; Conder, Michael J.
CORPORATE SOURCE: Biotechnology Section, Merck and Co., Inc., Elkton, VA, 22827, USA
SOURCE: Applied and Environmental Microbiology (1997), 63(4), 1307-1311
CODEN: AEMIDF; ISSN: 0099-2240
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An esterase from the fungus Clonostachys compactiuscula selectively **hydrolyzes** lovastatin, a clin. useful antihypercholesterolemic agent. Lovastatin or lovastatin-related compds. were required to induce the activity of the lovastatin 8'-(α-methylbutyryloxy) esterase. The 46-kDa esterase was purified from mycelial exts. by centrifugation and a single anion-exchange chromatog. separation Maximal lovastatin esterase activity was found at pH 9.0 to 9.6 and at 25 to 30°. The addition of 5 to 20% methanol resulted in greater lovastatin hydrolysis, while the addition of other solvents (ethanol, isopropanol, butanol, Et acetate, iso-Pr acetate, or tetrahydrofuran) decreased hydrolysis. Lovastatin was selectively **hydrolyzed** even in the presence of an excess of simvastatin, another antihypercholesterolemic agent that is structurally very similar to lovastatin. This lovastatin 8'-(α-methylbutyryloxy) esterase can be used to prepare a core intermediate for the generation of novel antihypercholesterolemic agents or to purify simvastatin prepared by C methylation of the 2(S)-methylbytyryloxy side chain of lovastatin.

IT **79902-63-9P**, Simvastatin
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(separation of lovastatin and simvastatin by enzymic removal of lovastatin using lovastain esterase from Clonostachys compactiuscula)

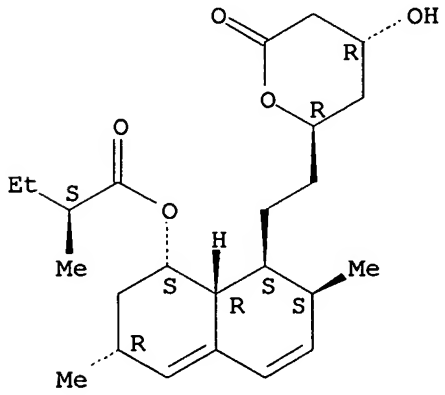
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **75330-75-5**, Lovastatin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(separation of lovastatin and simvastatin by enzymic removal of lovastatin using lovastain esterase from Clonostachys compactiuscula)
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

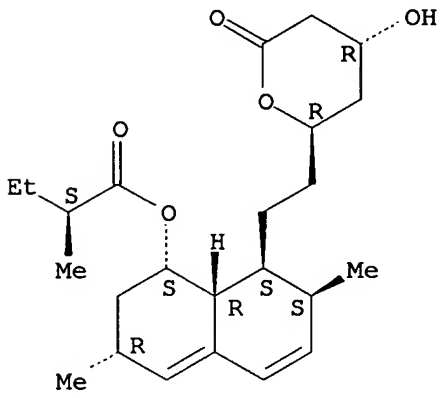
L8 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:114566 CAPLUS
DOCUMENT NUMBER: 114:114566
TITLE: Rate and equilibrium constants for acid-catalyzed **lactone** hydrolysis of HMG-CoA reductase inhibitors
AUTHOR(S): Kaufman, Michael J.
CORPORATE SOURCE: Pharm. Res. Dev., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: International Journal of Pharmaceutics (1990), 66(1-3), 97-106
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acid-catalyzed hydrolysis of mevalonolactone and several structurally

related hypocholesterolemic agents was studied in a pH 2.0 buffer at 37°. All of the reactions exhibited pseudo first-order kinetics from which the equilibrium constant and rate consts. for hydrolysis and **lactonization** were derived. Except for mevalonic acid **lactone**, all of the compds. reacted at essentially the same rate. Mevalonolactone **hydrolyzes** at a rate similar to the other compds. but relactonizes at a substantially faster rate; variable temperature kinetic studies indicate that this difference is due to both enthalpic and entropic factors. The hydrolysis data are used to simulate the extent of drug degradation that occurs in acidic gastric fluids following oral administration of these drugs.

IT **75330-75-5 79902-63-9**
RL: BIOL (Biological study)
(stomach acid-catalyzed hydrolysis of, kinetics of)

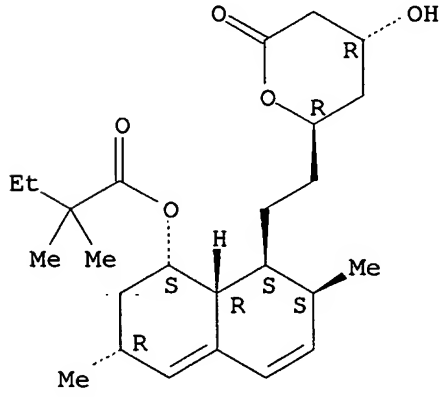
RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



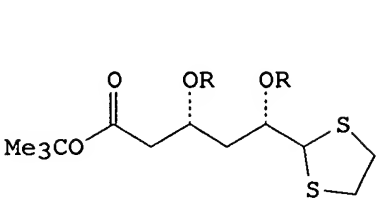
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:101787 CAPLUS

DOCUMENT NUMBER: 114:101787
TITLE: Synthesis of enantiomeric pure intermediate for the **lactone** portion of compactin and mevinolin
AUTHOR(S): Cardani, Silvia; Scolastico, Carlo; Villa, Roberto
CORPORATE SOURCE: Dip. Chim. Org. Ind., Univ. Milano, Milan, 20133, Italy
SOURCE: Tetrahedron (1990), 46(20), 7283-8
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:101787
GI



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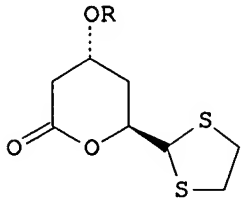


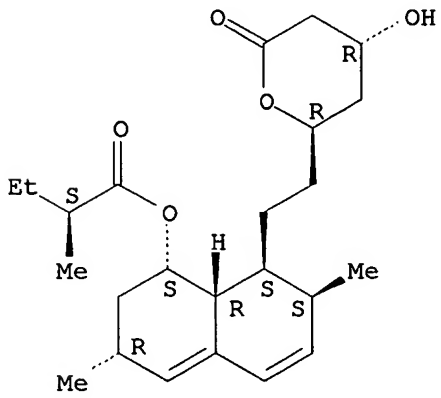
II

AB The diastereoselective synthesis of tert-Bu 3,5-dihydroxy-5-(1,3-dithiolan-2-yl)pentanoate I (R = H, Me3CMe2Si) starting from 3-[(R,S)-4-methyl-5-phenyl-3-tosyloxazol-2-yl]-2-propenal (i.e., a norephedrine derivative) was described. **Lactonization** of I (R = H) gave the resp. β-hydroxy **lactone** II (R = H); however, attempts to **hydrolyze** II (R = Me3CMe2Si) to give the resp. aldehyde failed. Hydrolysis of I (R = H) gave the resp. tert-Bu 4,5-dihydroxy-6-oxohexanoate, which is a synthetic building block for compactin or mevinolin (no data).

IT **75330-75-5**, Mevinolin
RL: RCT (Reactant); RACT (Reactant or reagent)
(Bu dihydroxyoxohexanoate as intermediate for, diastereoselective and enantioselective synthesis of)

RN 75330-75-5 CAPLUS
CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d his

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     (FILE 'HOME' ENTERED AT 09:32:13 ON 16 MAR 2006)

     FILE 'REGISTRY' ENTERED AT 09:32:24 ON 16 MAR 2006
L1             STRUCTURE UPLOADED
L2               3 S L1
L3              62 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 09:33:36 ON 16 MAR 2006
L4            4635 S L3 FULL
L5            3408 S L4 AND PY<2004
L6              31 S L5 AND HYDROLYZ?
L7              42 S L4 AND HYDROLYZ?
L8              14 S L7 AND LACTON?

=> log y
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                81.64     249.23

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                               -10.50     -10.50

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NEWS 5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
NEWS 6	DEC 14	CA/CAplus to be enhanced with updated IPC codes
NEWS 7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 13	JAN 30	Saved answer limit increased
NEWS 14	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 15	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 16	FEB 22	Status of current WO (PCT) information on STN
NEWS 17	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 18	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 19	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 20	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 21	FEB 28	TOXCENTER reloaded with enhancements
NEWS 22	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 23	MAR 01	INSPEC reloaded and enhanced
NEWS 24	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 25	MAR 08	X.25 communication option no longer available after June 2006

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 09:39:40 ON 16 MAR 2006

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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DICTIONARY FILE UPDATES: 14 MAR 2006 HIGHEST RN 876856-38-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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Please note that search-term pricing does apply when conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

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http://www.cas.org/ONLINE/UG/regprops.html

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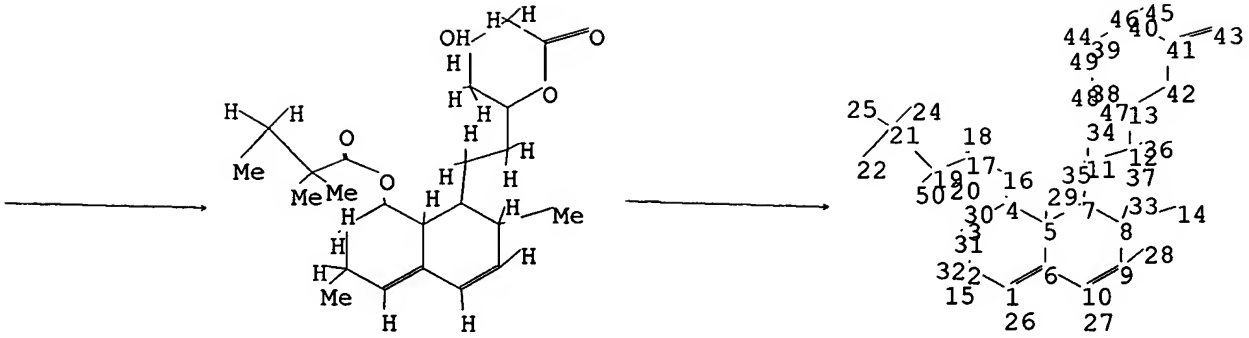

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34 35 36 37 43 44 45 46 47 48 49 50
ring nodes :
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38-48 39-49 40-45 40-46

G1:H,CH3

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11:CLASS 12:CLASS 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS
36:CLASS 37:CLASS 38:Atom 39:Atom 40:Atom 41:Atom 42:Atom 43:CLASS 44:CLASS
45:CLASS 46:CLASS 47:CLASS 48:CLASS 49:CLASS 50:CLASS
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L1 STRUCTURE UPLOADED

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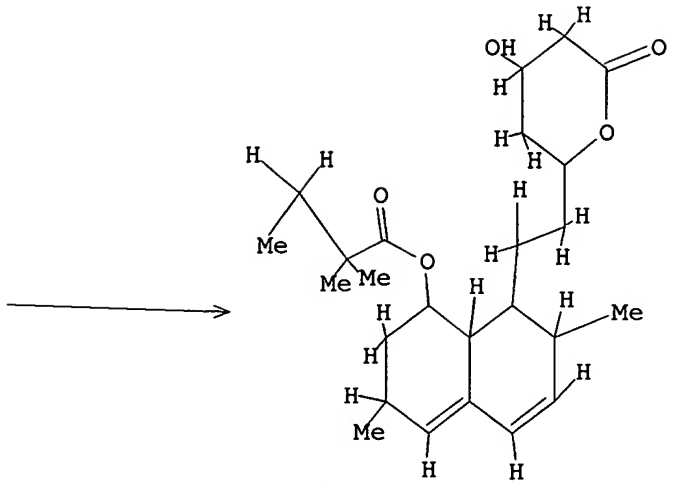
L1 STR



G1 H,Me

Structure attributes must be viewed using STN Express query preparation.

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.44       0.65

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This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> s l1
SAMPLE SEARCH INITIATED 09:40:55 FILE 'CASREACT'
SCREENING COMPLETE -      5 REACTIONS TO VERIFY FROM        1 DOCUMENTS

100.0% DONE       5 VERIFIED       5 HIT RXNS                      1 DOCS
SEARCH TIME: 00.00.01
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FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED VERIFICATIONS:          5 TO      234
PROJECTED ANSWERS:                1 TO       79

L2            1 SEA SSS SAM L1 (     5 REACTIONS)

=> s l1 full
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100.0% DONE     312 VERIFIED     123 HIT RXNS                    33 DOCS
SEARCH TIME: 00.00.01

L3           33 SEA SSS FUL L1 (   123 REACTIONS)

=> d fhit ibib abs tot

L3   ANSWER 1 OF 33  CASREACT  COPYRIGHT 2006 ACS on STN


RX(5) OF 15      ...L  ===>  N
```
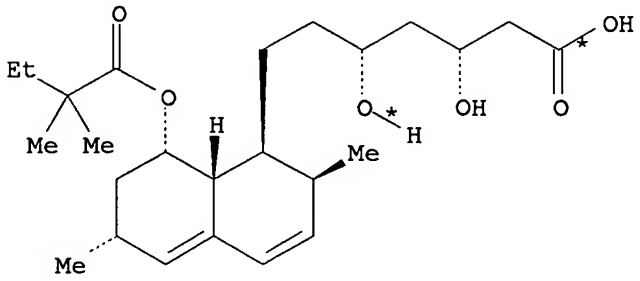
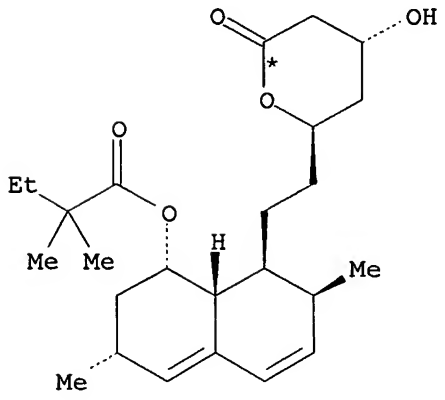



● NH_3

L → (5) →



N
YIELD 25%

RX(5) RCT L 139893-43-9

STAGE(1)
RGT O 1310-73-2 NaOH
SOL 67-56-1 MeOH
CON 2 hours, reflux

STAGE(2)
RGT P 7647-01-0 HCl
SOL 7732-18-5 Water
CON pH 5

STAGE(3)
SOL 108-88-3 PhMe
CON 6 hours, reflux

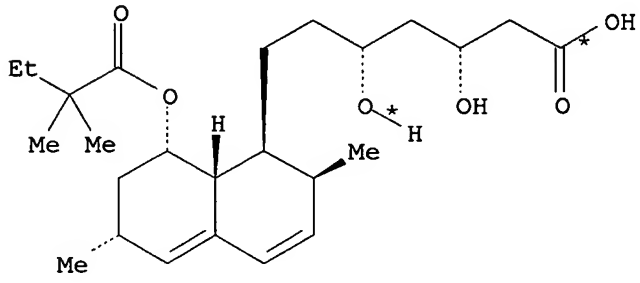
PRO N **79902-63-9**

ACCESSION NUMBER: 143:306052 CASREACT
TITLE: Semi-synthesis of simvastatin
AUTHOR(S): Ren, Sumei; Xu, Jie; Sun, Mingkun
CORPORATE SOURCE: Marine Drug and Food Institute, Ocean University of China, Qingdao, 266003, Peop. Rep. China
SOURCE: Zhongguo Yaowu Huaxue Zazhi (2003), 13(1), 38-39
CODEN: ZYHZEF; ISSN: 1005-0108
PUBLISHER: Zhongguo Yaowu Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Simvastatin was semi-synthesized from lovastatin through the aminolysis, selective silylation, alkylation, and desilylation reactions. Its structure was identified by elementary anal., IR spectrum, UV spectrum, NMR spectrum, and MS spectrum.

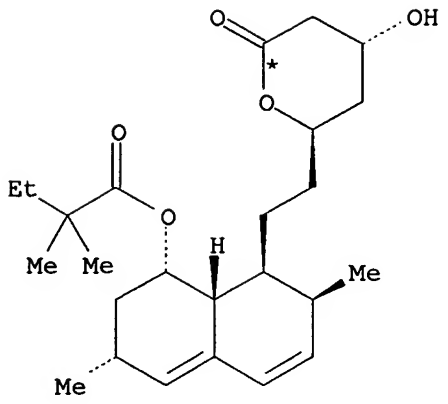
L3 ANSWER 2 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(6) OF 21 ...P ===> **V**



● NH_3

P (6) →



V
YIELD 97%

RX(6) RCT P 139893-43-9
PRO V **79902-63-9**
SOL 108-88-3 PhMe
CON reflux

ACCESSION NUMBER: 143:248205 CASREACT
TITLE: Improved process for producing simvastatin
INVENTOR(S): Bhadwal, Paramvir; Jain, Pratima; Thaper, Rajesh Kumar; Dubey, Sushil Kumar; Khanna, Jag Mohan
PATENT ASSIGNEE(S): Jubilant Organosys Limited, India
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005077928	A1	20050825	WO 2005-IN43	20050211

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IN 2004-DE201 20040212
OTHER SOURCE(S): MARPAT 143:248205
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

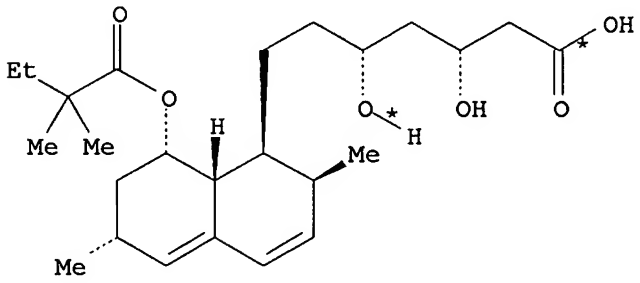
AB Disclosed herein is an industrially feasible process for producing HMG-CoA reductase inhibitor, simvastatin (I) via an improved acylation process using lovastatin ammonium salt as a starting material. The process

comprising treating lovastatin ammonium salt with a base to give II, lactonization of II gave III, selectively protecting the hydroxyl group of III followed by acylation of the protected derivs. with dimethylbutyrylchloride using potassium halide in presence of a solvent gave IV, deprotection of IV followed by hydrolysis gave the simvastatin ammonium salt derivative, which underwent lactonization to give simvastatin.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

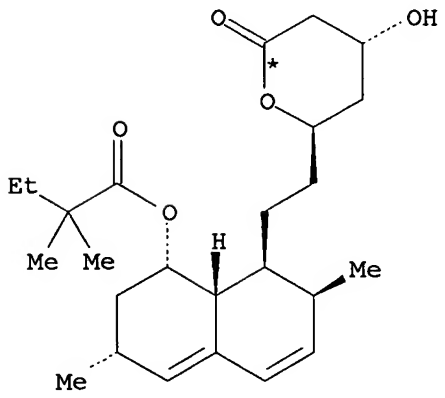
L3 ANSWER 3 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(4) OF 12 ...L ===> **R**



● NH_3

L (4) ⟶



R

RX(4) RCT L 139893-43-9

STAGE(1)
SOL 108-88-3 PhMe
CON 5 hours, 100 deg C

STAGE(2)
RGT S 7440-44-0 Carbon
CON 30 minutes, 25 deg C

STAGE(3)
SOL 110-82-7 Cyclohexane
CON SUBSTAGE(1) 20 minutes, reflux
SUBSTAGE(2) 3 hours, 10 deg C

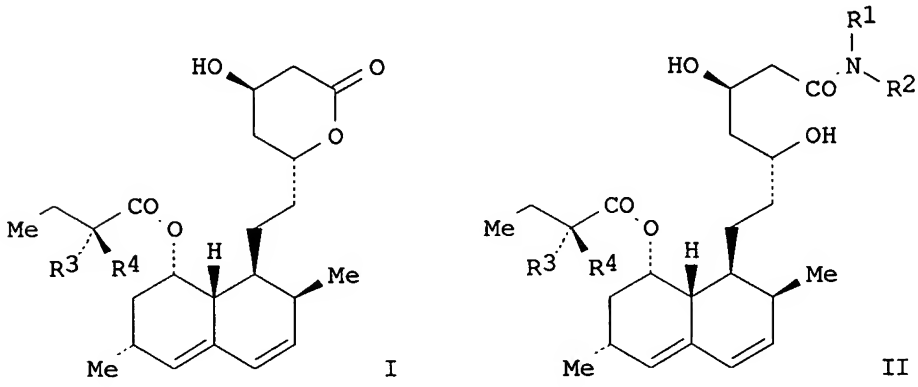
PRO R **79902-63-9**
NTE activated charcoal used stage 2

ACCESSION NUMBER: 143:133225 CASREACT
TITLE: A novel process for the preparation of simvastatin
INVENTOR(S): Parthasaradhi Reddy, Bandi; Rathnakar Reddy, Kura; Raji Reddy, Rapolu; Muralidhara Reddy, Dasari; Subash Chander Reddy, Kesireddy
PATENT ASSIGNEE(S): Hetero Drugs Limited, India
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005066150	A1	20050721	WO 2004-IN3	20040102

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2004-IN3 20040102
OTHER SOURCE(S): MARPAT 143:133225
GI

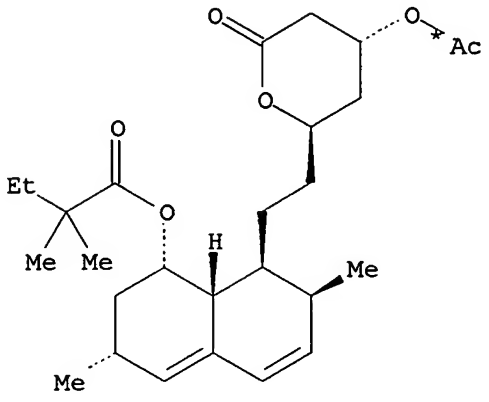


AB A process for manufacturing simvastatin I (R3 = R4 = Me) was disclosed and comprised the preparation of amide intermediates II [R1 = alkyloxyalkyl, alkylthioalkyl, alkoxyarylalkyl, alkylthioarylalkyl, alkoxycycloalkyl, alkylthiocycloalkyl, etc.] and a subsequent methylation/lactonization reaction sequence. Thus, lovastatin I (R3 = H, R4 = Me) was reacted with methoxyethylamine to give amide II [R1 = H, R2 = (CH2)2OMe, R3 = H, R4 = Me] which was subsequently alpha methylated on 2-methylbutyryl side chain to form II [R1 = H, R2 = (CH2)2OMe, R3 = R4 = Me] which was in turn hydrolyzed and lactonized to produce simvastatin of high purity.

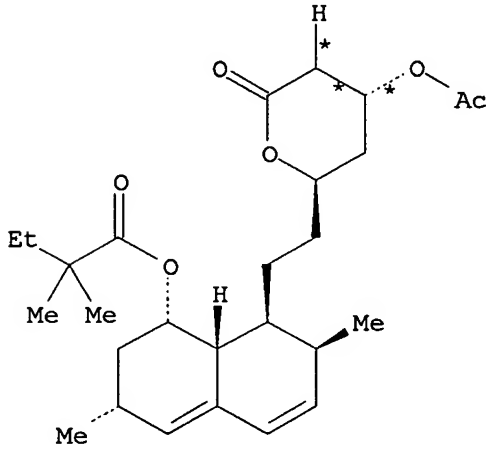
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

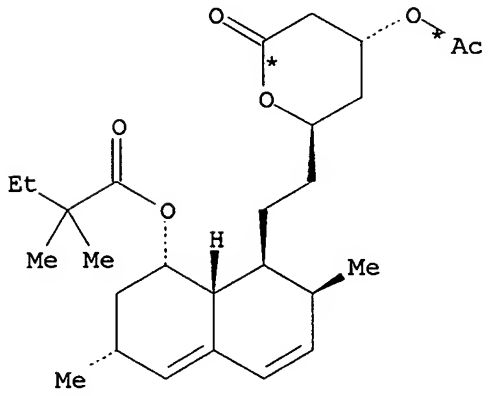
RX(1) OF 42 ...3 A ===> **B** + C + D...



A



A



A

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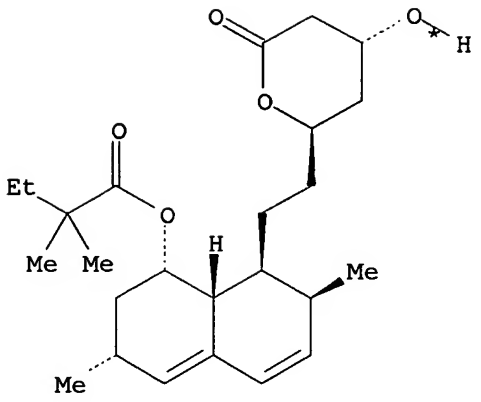
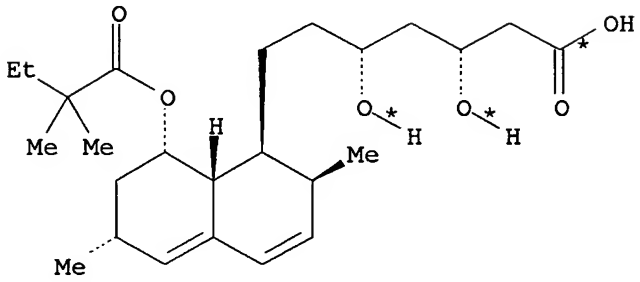
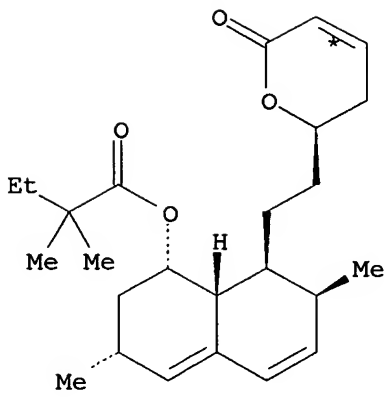


B
YIELD 91%



C
YIELD 5%



D
YIELD 4%

RX(1) RCT A 145576-25-6

STAGE(1)
RGT E 126-72-7 1-Propanol, 2,3-dibromo-, phosphate (3:1)
SOL 7732-18-5 Water, 67-56-1 MeOH
CON room temperature

STAGE(2)
CAT 851427-32-2 4: PN: WO2005040107 SEQID: 4 unclaimed protein
SOL 7732-18-5 Water
CON room temperature

STAGE(3)
RGT F 1336-21-6 NH4OH
SOL 7732-18-5 Water
CON room temperature

STAGE(4)
SOL 108-88-3 PhMe
CON overnight, room temperature

PRO B **79902-63-9**, C 121009-77-6, D 210980-68-0
NTE biotransformation, enzymic [esterase SEQ ID NO:4 (encoded by SEQ ID NO:3)]; first three stages buffer; third stage DasGip STIRRER-PRO pH-stat system

ACCESSION NUMBER: 142:463506 CASREACT
TITLE: Methods for making simvastatin and intermediates from lovastatin
INVENTOR(S): Morgan, Brian; Burk, Mark; Levin, Michael; Zhu, Zoulin; Chaplin, Jennifer; Kustedjo, Karen; Huang, Zilin; Greenberg, William
PATENT ASSIGNEE(S): Diversa Corporation, USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005040107	A2	20050506	WO 2004-US34913	20041020

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

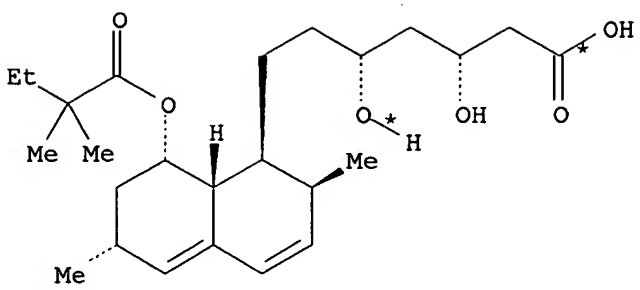
PRIORITY APPLN. INFO.: US 2003-513237P 20031021
US 2004-542100P 20040204
OTHER SOURCE(S): MARPAT 142:463506
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides synthetic chemical and chemoenzymic methods of producing simvastatin (I) and various intermediates, e.g., triol II, acylates III [R = H, Me, (un)branched, (un)substituted C1-20-alkyl, (un)substituted Ph (especially Ph, C6H4NO2-4), OR'; R' = any of previous R] and dimethylbutyrates IV. The method comprises: (a) enzymic hydrolysis of lovastatin, lovastatin acid or salt to triol acid (II) or triol acid salt; (b) lactonization and acylation of the triol acid to form 4-acetyl lactone III (R = Me), wherein the acylation protects a 4-position hydroxyl (4'-OH) on the lactone ring by regioselective acylation of the 4'-OH; (c) enzymic acylation of an 8-position hydroxyl (8'-OH) of the 4-acetyl lactone III (R = Me) to form 4-acetylsimvastatin (IV; R = Me); and (d) selectively removing the acyl group at the 4'-position either chemical or enzymically, thereby yielding I. In one aspect, enzymes such as hydrolases, e.g., esterases, are used in the methods of the invention.

L3 ANSWER 5 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 3 A ===> **B**



● NH_3

A

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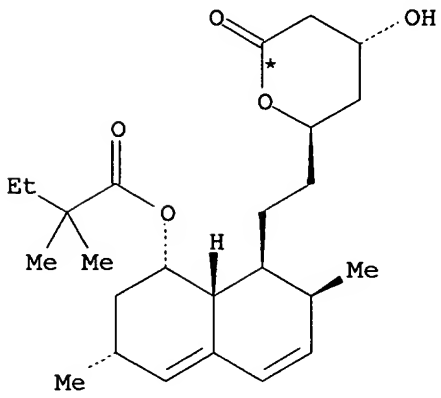


B

RX(1) RCT A 139893-43-9

STAGE(1)
CAT 25013-16-5 Phenol, (1,1-dimethylethyl)-4-methoxy-
SOL 75-05-8 MeCN
CON room temperature -> -20 deg C

STAGE(2)
RGT C 7664-93-9 H2SO4
CON 30 minutes, -17 - -22 deg C

PRO B **79902-63-9**
NTE TLC monitored

ACCESSION NUMBER: 142:197756 CASREACT
TITLE: Lactonization process for the production of statin lactones
INVENTOR(S): Chandrapa, Ravindra; Poornaprajna, Achraya; Ganesh, Sambasivam
PATENT ASSIGNEE(S): Biocon Limited, India
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005012279	A1	20050210	WO 2003-IN264	20030804

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2003-IN264 20030804
OTHER SOURCE(S): MARPAT 142:197756
GI

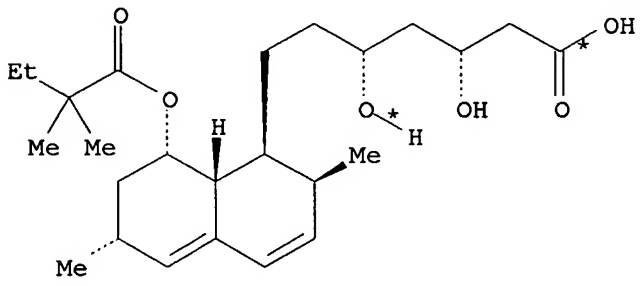
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for preparation of lactone statins I [G = (un)substituted alkyl, aryl, heteroaryl] comprises reacting a statin acid or salt II [X = H, metal, amine] with sulfuric acid, where the sulfuric acid is added in one portion, at less than 0.8 equiv of the statin salt or acid, at less than -15° for <1 h in a water-miscible solvent (e.g., acetonitrile). Thus, simvastatin (III) was prepared from simvastatin ammonium salt (IV·+NH4) in MeCN containing butylated hydroxanisole to which H2SO4 was added.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

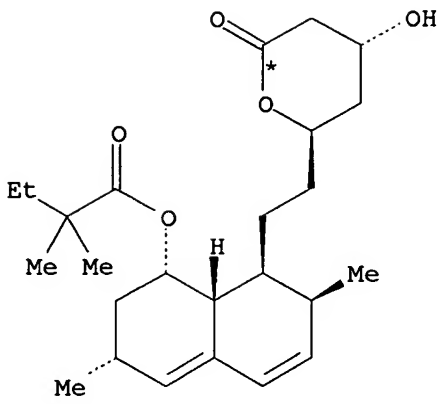
L3 ANSWER 6 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(3) OF 6 ...I ===> o



● NH_3

I (3) →



O
YIELD 92%

RX(3) RCT I 139893-43-9
PRO O **79902-63-9**
SOL 108-88-3 PhMe
CON 4 hours, 90 deg C

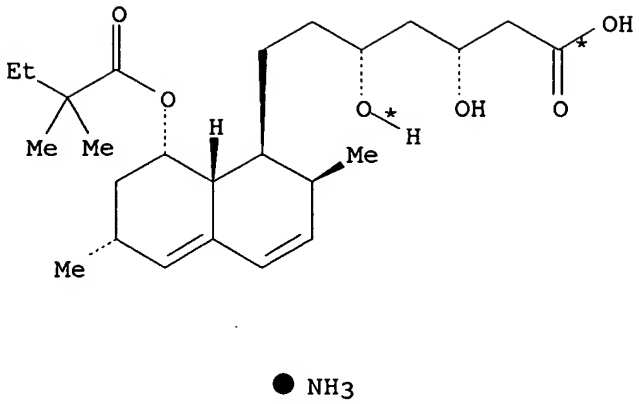
ACCESSION NUMBER: 141:243202 CASREACT
TITLE: A convenient procedure for the methylation of lovastatin. Synthesis of simvastatin
AUTHOR(S): Dabak, Kadir; Keskin, Hulya
CORPORATE SOURCE: Department of Research and Development, Eczacibasi Ozgun Kimya, Organize Sanayi Bolgesi, Tekirdag, 59500, Turk.
SOURCE: Heterocyclic Communications (2004), 10(1), 29-34
CODEN: HCOMEX; ISSN: 0793-0283
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new synthetic method for the preparation of the cholesterol lowering drug simvastatin from the naturally occurring lovastatin is reported. The synthesis relies upon deactivation of the α-carbon of the δ-lactone via conversion of the lactone group of lovastatin to its carboxylic acid-amine salt derivative and then methylation of the 2-methylbutyrate-side chain of simvastatin.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

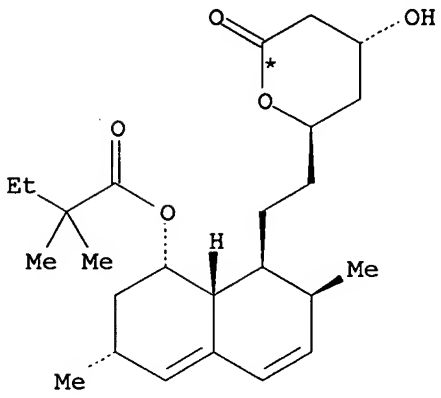
L3 ANSWER 7 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 10 ...A ===> **B**



A

(1)



B

RX(1) RCT A 139893-43-9
PRO B **79902-63-9**
SOL 108-88-3 PhMe
CON reflux

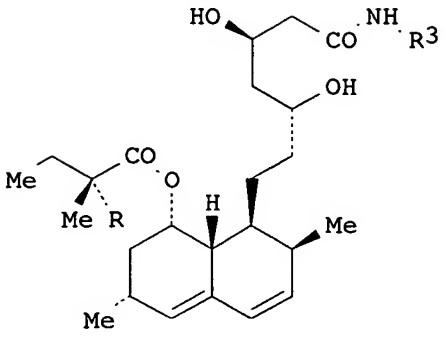
ACCESSION NUMBER: 141:6967 CASREACT
TITLE: Process for the preparation of simvastatin from lovastatin or mevinolinic acid
INVENTOR(S): Kumar, Yatindra; Thaper, Rajesh Kumar; Misra, Satya Nand; Kumar, S. M. Dileep; Khanna, Jag Mohan
PATENT ASSIGNEE(S): Ranbaxy Laboratories Limited, India
SOURCE: Indian, 12 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 184969	A	20001014	IN 1997-DE175	19970124
HR 970435	B1	20011231	HR 1997-970435	19970807
CZ 290672	B6	20020911	CZ 1997-2649	19970820
SK 283319	B6	20030603	SK 1997-1167	19970825

PRIORITY APPLN. INFO.: IN 1997-CA175 19970124
IN 1997-DE175 19970124
US 1997-816573 19970313

OTHER SOURCE(S): MARPAT 141:6967

GI

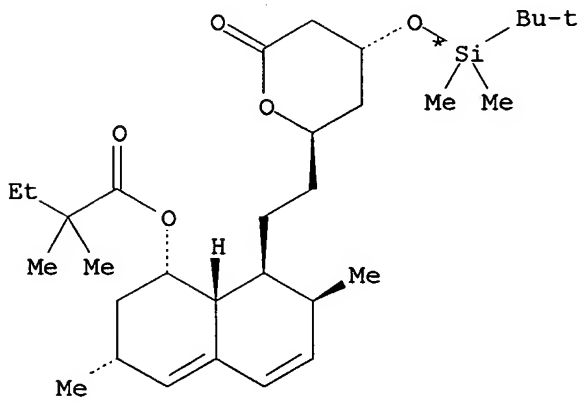


I

AB A novel process was disclosed for the preparation of simvastatin which comprised reacting lovastatin or mevinolinic acid with alkylamine of the formula R3NH2 (R3 = Bu, cyclopropyl, alkyl) to yield alkyl amide compds. I (R = H, Me; R3 = Bu, cyclopropyl, alkyl) which were then reacted with a methylating agent like MeI in the presence of a base like lithium pyrrolide to give I (R = Me; R3 = Bu, cyclopropyl, alkyl) which are further reacted with a strong base like sodium hydroxide to cleave the amide linkage and then treated with ammonium hydroxide to precipitate simvastatin ammonium salt which on further heating with an organic solvent give simvastatin.

L3 ANSWER 8 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 1 A ===> **B**



A

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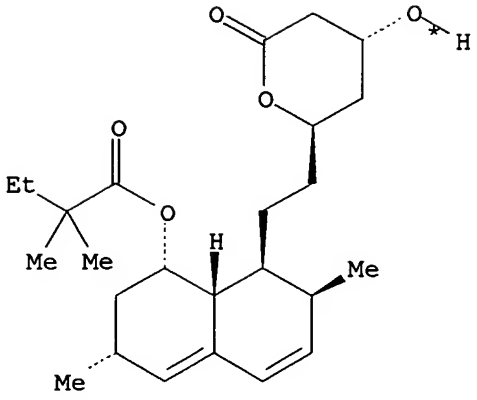


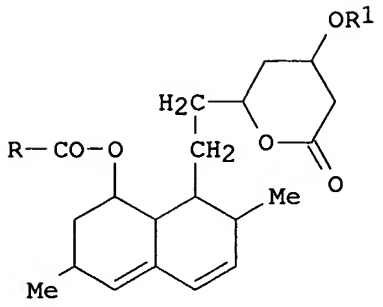
B
YIELD 76%

RX(1) RCT A 79902-59-3
RGT C 121-44-8 Et3N
PRO B **79902-63-9**
SOL 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 46 hours, room temperature
NTE optimization study

ACCESSION NUMBER: 139:307681 CASREACT
TITLE: Process for the preparation of 4-oxytetrahydropyran-2-ones
INVENTOR(S): Zupancic, Silvo; Krasovec, Dusan; Zupet, Pavel
PATENT ASSIGNEE(S): Krka Tovarna Zdravil, D.D. Novo Mesto, Slovenia
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080591	A1	20031002	WO 2003-SI9	20030317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
SI 21187	C	20031031	SI 2002-86	20020326
AU 2003214791	A1	20031008	AU 2003-214791	20030317
EP 1487814	A1	20041222	EP 2003-710622	20030317
EP 1487814	B1	20050810		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005523303	T2	20050804	JP 2003-578346	20030317
AT 301648	E	20050815	AT 2003-710622	20030317
US 2005182263	A1	20050818	US 2003-509611	20030317
PRIORITY APPLN. INFO.:			SI 2002-86	20020326

OTHER SOURCE(S): MARPAT 139:307681
GI



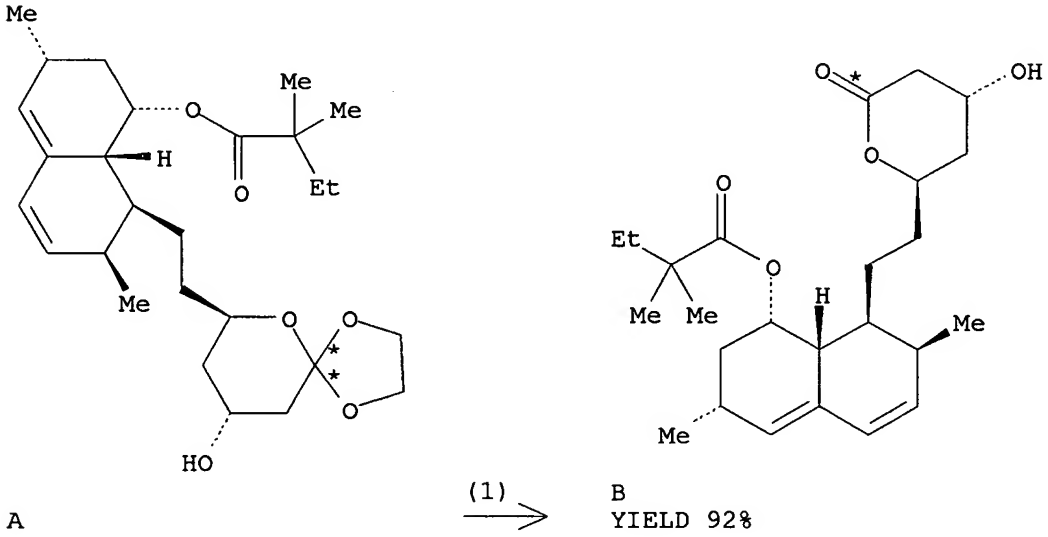
I

AB A process for the preparation of inhibitors of HMG-CoA reductase, such as simvastatin, from 4-silyloxytetrahydropyran-2-ones with NEt3.3HF being used as the desilylation reagent is described. The reaction was performed in organic solvents, a mixture thereof or without solvents. It is characteristic of this reaction that no addnl. impurities were obtained and that it takes place without the use of addnl. catalysts and with low excesses of the reagent.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 13 ...A ===> **B**



A (1) B YIELD 92%

RX(1) RCT A 479482-40-1
RGT C 7647-01-0 HCl
PRO B **79902-63-9**
SOL 109-99-9 THF, 7732-18-5 Water
CON 3 hours, room temperature

ACCESSION NUMBER: 139:164642 CASREACT
TITLE: A new synthesis of the antihypercholesterolemic agent

simvastatin

AUTHOR(S): Dabak, Kadir; Adiyaman, Mustafa
CORPORATE SOURCE: Turk.
SOURCE: Helvetica Chimica Acta (2003), 86(3), 673-677
CODEN: HCACAV; ISSN: 0018-019X
PUBLISHER: Verlag Helvetica Chimica Acta
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

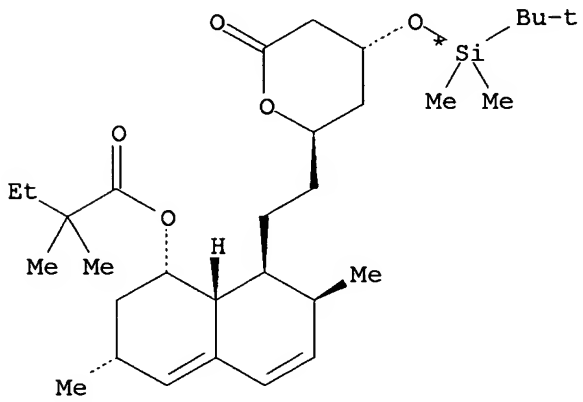
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A new preparation of the cholesterol-lowering drug simvastatin (I) from the naturally occurring lovastatin (II) is reported. The synthesis employs first the protection of the OH group of lovastatin and then the protection of the lactone C:O group to prevent enolization via conversion to the orthoesters III (R = Ph, Me3C). Alkylation of the 2-methylbutyrate side chain is then successfully achieved. Removal of the protecting groups affords simvastatin.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

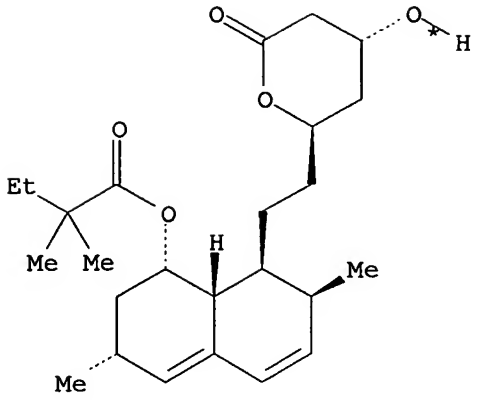
L3 ANSWER 10 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(5) OF 15 ...N ===> **R**



(5)

N



R
YIELD 91%

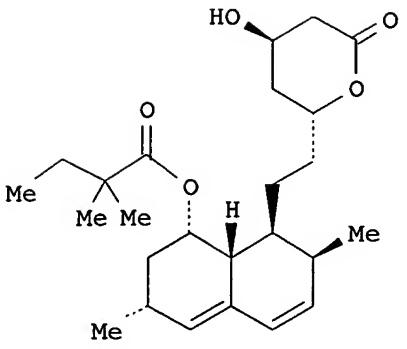
RX(5) RCT N 79902-59-3
RGT S 429-41-4 Bu4N.F
PRO R **79902-63-9**
SOL 109-99-9 THF, 64-19-7 AcOH
CON 48 hours, room temperature

ACCESSION NUMBER: 139:100975 CASREACT
TITLE: Process for the preparation of simvastatin
INVENTOR(S): Lee, Jaeheon; Ha, Taehee; Park, Chulhyun; Lee, Hoechul; Lee, Gwansun; Chang, Youngkil
PATENT ASSIGNEE(S): Hanmi Pharm. Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057684	A1	20030717	WO 2002-KR2434	20021226
W: AU, CA, CN, HU, IN, JP, US				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR				
KR 2003060425	A	20030716	KR 2002-1118	20020109
AU 2002359034	A1	20030724	AU 2002-359034	20021226
EP 1463723	A1	20041006	EP 2002-793514	20021226
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, CY, TR, BG, CZ, EE, SK				
US 2005080275	A1	20050414	US 2003-501007	20021226
JP 2005514419	T2	20050519	JP 2003-557999	20021226
PRIORITY APPLN. INFO.:			KR 2002-1118	20020109
			WO 2002-KR2434	20021226

OTHER SOURCE(S): MARPAT 139:100975

GI



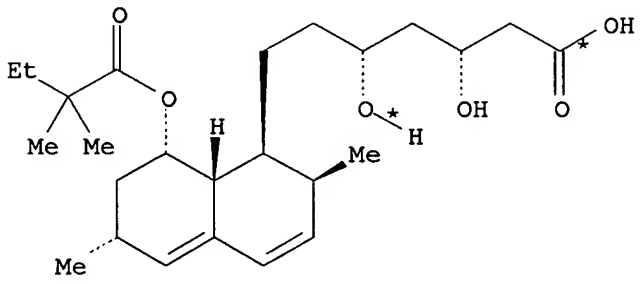
I

AB Highly pure simvastatin (I) can be prepared economically in a high yield using the method comprising the steps of treating lovastatin with potassium hydroxide dissolved in a mixture of water and methanol to obtain a triol acid; relactonizing the triol acid, and protecting the hydroxy group on the lactone ring; and acylating the resulting compound with 2,2-dimethylbutyryl chloride or 2,2-dimethylbutyryl bromide in the presence of an acylation catalyst in an organic solvent, followed by removing the silyl protecting group on the lactone ring to obtain simvastatin.

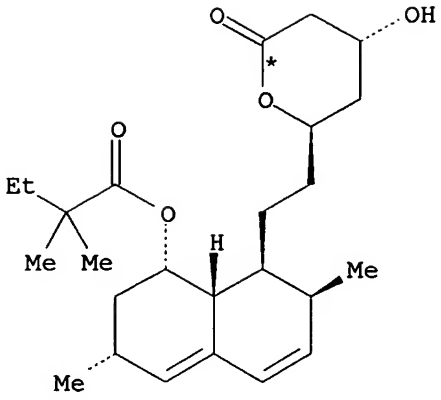
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(2) OF 4 E ===> **F**



E



F
YIELD 88%

RX(2) RCT E 139893-43-9
PRO F **79902-63-9**
SOL 75-09-2 CH2Cl2, 75-05-8 MeCN
CON 3 hours, 80 deg C
NTE under nitrogen

ACCESSION NUMBER: 139:6712 CASREACT
TITLE: Process for preparation of lovastatin and simvastatin by lactonization
INVENTOR(S): Lee, Kwang-hyeg; Kim, Jin-wan; Choi, Kwang-do; Lee, Sang-ho; Cho, Hong-suk
PATENT ASSIGNEE(S): CJ Corporation, S. Korea
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1316552	A1	20030604	EP 2002-26916	20021203
EP 1316552	B1	20060222		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
KR 2003045340	A	20030611	KR 2001-75991	20011203
WO 2003048149	A1	20030612	WO 2002-KR2095	20021111
W: AE, AG, AL, AM, AT, AZ, BA, BB, BG, BY, BZ, CH, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003109723	A1	20030612	US 2002-295300	20021114
US 6906204	B2	20050614		
CA 2413235	AA	20030603	CA 2002-2413235	20021129
CN 1425661	A	20030625	CN 2002-153037	20021129
JP 2003183271	A2	20030703	JP 2002-350255	20021202
BR 2002004943	A	20040615	BR 2002-4943	20021202
PRIORITY APPLN. INFO.:			KR 2001-75991	20011203

OTHER SOURCE(S): MARPAT 139:6712

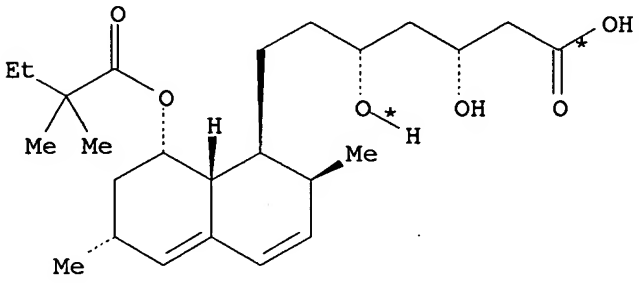
AB The present invention relates to a processing method for preparing lovastatin and simvastatin which comprises the steps of (1) performing lactonization of mevinic acid and its homologous compds. in the presence of a mixed organic solvent without an acid catalyst through nitrogen sweep; and (2) crystallization

In the process lovastatin and simvastatin can be produced in a high yield with high purity and heterodimers formed as a byproduct can be reduced remarkably. Therefore, the processing method of the present invention can be convenient and economical.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

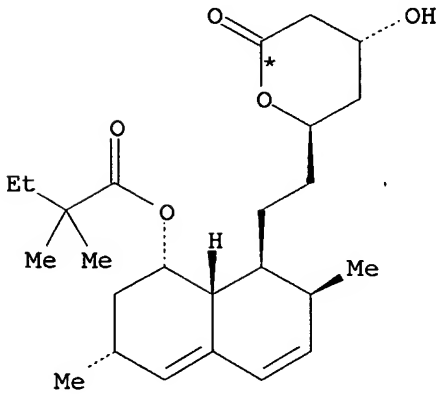
RX(1) OF 2 A ===> **B**



● NH_3

A

(1) →



B

YIELD 94%

RX(1) RCT A 139893-43-9

STAGE(1)
RGT C 7487-88-9 MgSO4
SOL 108-88-3 PhMe

CON 3 hours, 100 - 110 deg C

STAGE(2)
RGT D 7440-44-0 Carbon
CON 30 minutes, 25 deg C

STAGE(3)
SOL 110-82-7 Cyclohexane
CON 3 hours, 35 deg C

PRO B **79902-63-9**

ACCESSION NUMBER: 138:221390 CASREACT
TITLE: Process of lactonization and crystallization in the preparation of highly purified statins
INVENTOR(S): Lee, Kwang-Hyeg; Kim, Jin-Wan; Yoon, Myeong-Sik; Choi, Kwang-Do; Lee, Sang-Ho; Cho, Hong-Suk
PATENT ASSIGNEE(S): Cheil Jedang Corporation, S. Korea
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1288212	A1	20030305	EP 2002-15509	20020710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
KR 2003018202	A	20030306	KR 2001-51796	20010827
WO 2003018570	A1	20030306	WO 2002-KR1281	20020706
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003050482	A1	20030313	US 2002-200174	20020723
US 6649775	B2	20031118		
CN 1406938	A	20030402	CN 2002-127086	20020729
JP 2003096071	A2	20030403	JP 2002-245931	20020826
PRIORITY APPLN. INFO.:			KR 2001-51796	20010827

OTHER SOURCE(S): MARPAT 138:221390
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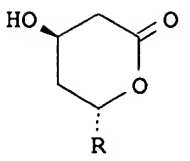
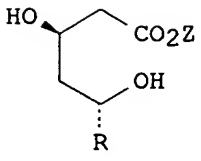
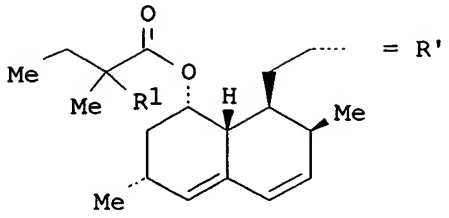


I



II

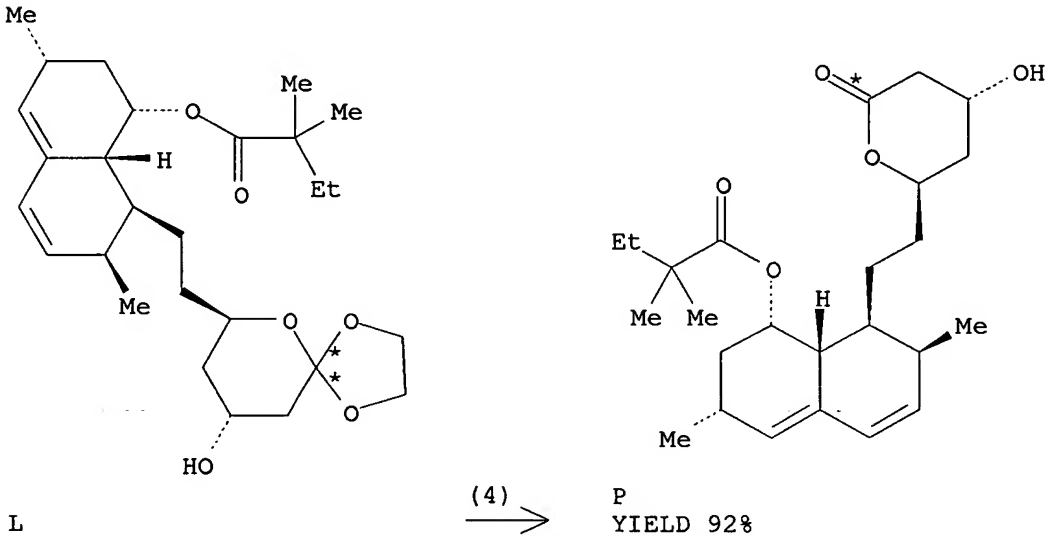


AB The present invention relates to a process for preparing lovastatin (I; R = R', R1 = α-H) and simvastatin (I; R = R', R1 = Me) which comprises a step of (1) performing a lactonization of mevinic acid analogs II (Z = H, NH4, metal cation) in the presence of a dehydrating agent and without an acid catalyst under nitrogen sweep; and then a step of (2) making crystals at a high temperature In the process of the present invention, I can be produced highly purified in a high yield and, especially, heterodimers formed as a byproduct can be reduced in an amount remarkably. Therefore, the process of the present invention is convenient and economical.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(4) OF 13 ...L ===> **P**



L (4) P

YIELD 92%

RX(4) RCT L 479482-40-1

RGT Q 7647-01-0 HCl
PRO P **79902-63-9**
SOL 7732-18-5 Water, 109-99-9 THF
CON 3 hours, room temperature

ACCESSION NUMBER: 138:55801 CASREACT
TITLE: Process for the preparation of simvastatin from lovastatin
INVENTOR(S): Dabak, Kadir; Adiyaman, Mustafa
PATENT ASSIGNEE(S): Eos Eczacibasi Ozgun Kimyasal Urunler Sanayi Ve Ticaret A.S., Turk.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

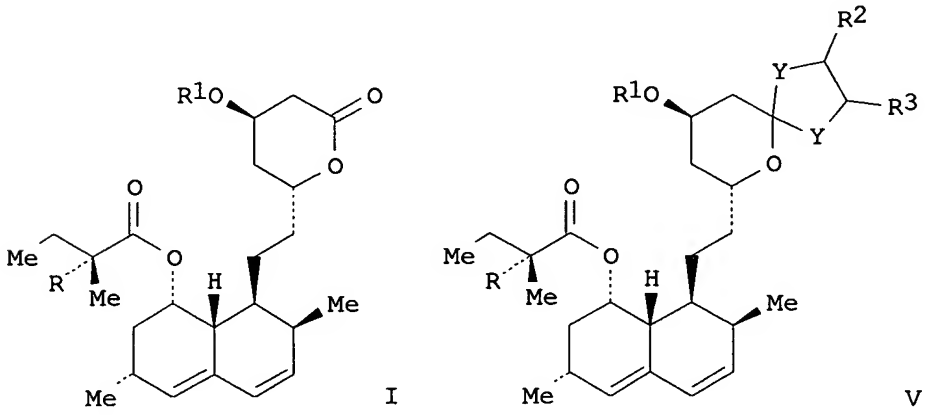
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000673	A2	20030103	WO 2002-TR24	20020619
WO 2003000673	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

TR 200101687	A2	20040121	TR 2001-20010168	20010621
PRIORITY APPLN. INFO.:			TR 2001-1687	20010621

OTHER SOURCE(S): MARPAT 138:55801
GI



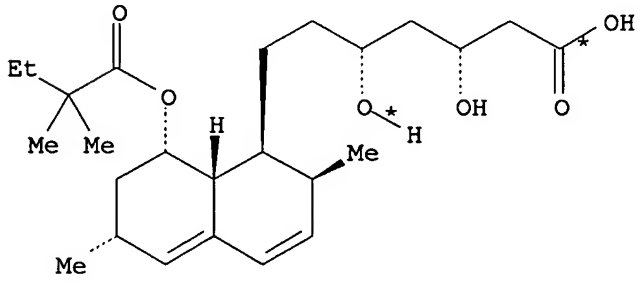
I V

AB The present invention discloses a process for preparation of simvastatin I [R = Me, R1 = H (II)] from lovastatin I [R = R1 = H (III)], by reacting III with a hydroxy protecting group, R1X (R1 = aroyl, acyl; X = Cl, Br, I) to provide I [R = H; R1 = aroyl, acyl (IV)]. The carbonyl in the lactone of IV was protected as an ortho ester derivative V [R = H; R2, R3 = H, aliphatic, aromatic; Y = O, S], which on methylation with MeZ/M+R4R5N [M = Li, Na, K; R4, R5 = Me, iso-Pr, trimethylsilyl, cycloalkyl; Z = X], and subsequent hydrolysis afforded II. Thus, III was reacted with benzoyl chloride to afford I [R = H, R1 = COPh], which on condensation with ethylene glycol

afforded diprotected lovastatin derivative V [R = H; R1 = COPh; R2,R3 = H; Y = O (VI)]. Methylation of VI with Me iodide in presence of n-butyllithium and pyrrolidine provided simvastatin orthoester derivative V [R = Me, R1-R3 = H; Y = O], which on hydrolysis with dilute acid afforded II. The main feature of this invention was the protection of the carboxyl in the lactone of III as an ortho ester and alkylation of an α-carbon to a carboxyl group.

L3 ANSWER 14 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

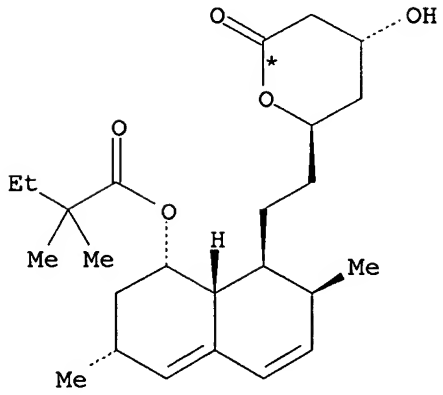
RX(1) OF 15 ...A ===> B



● NH_3

A

(1) →



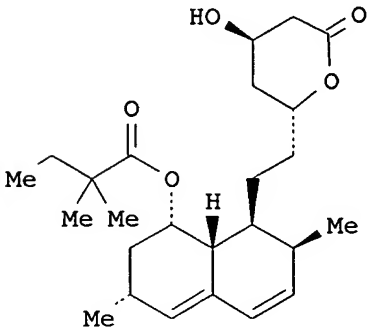
B
YIELD 91%

RX(1) RCT A 139893-43-9
PRO B **79902-63-9**
SOL 1330-20-7 Xylene
CON SUBSTAGE(1) 138 - 140 deg C
SUBSTAGE(2) 30 minutes, 138 - 140 deg C
SUBSTAGE(3) 140 deg C -> 30 deg C
NTE thermal, alternative prepn. gave lower yield
ACCESSION NUMBER: 138:4469 CASREACT
TITLE: Preparation of simvastatin from simvastatin acid derivatives via lactonization in an organic solvent

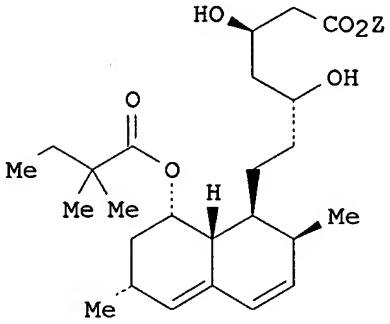
INVENTOR(S): Ramesh, Dandala; Sonny, Sebastian; Sanapureddy, Jagan Mohan Reddy; Meenakshisunderam, Sivakumaran
PATENT ASSIGNEE(S): Aurobindo Pharma Limited, India
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094804	A1	20021128	WO 2002-IN122	20020516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1294706	A1	20030326	EP 2002-749274	20020516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
SI 21235	C	20031231	SI 2002-20005	20020516
JP 2004520445	T2	20040708	JP 2002-591477	20020516
BG 107475	A	20040130	BG 2003-107475	20030117
US 2004019225	A1	20040129	US 2003-440537	20030519
US 6797831	B2	20040928		
PRIORITY APPLN. INFO.:			IN 2001-MA401	20010518
			IN 2001-CH401	20010518
			WO 2002-IN122	20020516

GI



I



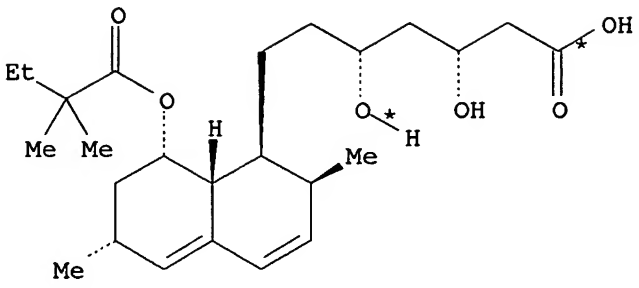
II

AB The present invention discloses a process for preparation of simvastatin (I) from simvastatin acid derivs., such as II [Z = H, NH4], via heating in an organic solvent selected from xylenes, ethylbenzene and mixts. thereof. Thus, II [Z = NH4] (also prepared) was added to xylenes and the reaction mixture was refluxed at 130 to 140 °C with constant nitrogen purging for 30 min to afford I (yield = >94.8 %).

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

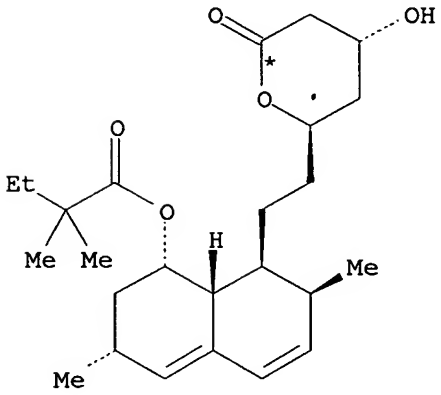
RX(1) OF 1 A ===> B



● NH_3

A

(1) →



B
YIELD 89%

RX(1) RCT A 139893-43-9

STAGE(1)
SOL 75-05-8 MeCN, 64-19-7 AcOH

STAGE(2)
SOL 7732-18-5 Water

PRO B **79902-63-9**

ACCESSION NUMBER: 137:384690 CASREACT
TITLE: Preparation of simvastatin from simvastatin acid derivs. via lactonization
INVENTOR(S): Ramesh, Dandala; Sonny, Sebastian; Dandala, Subramanyam; Meenakshisunderam, Sivakumaran
PATENT ASSIGNEE(S): Aurobindo Pharma Limited, India
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094803	A1	20021128	WO 2002-IN121	20020516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
SI 21234	C	20031231	SI 2002-20004	20020516
EP 1387835	A1	20040211	EP 2002-743614	20020516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004520444	T2	20040708	JP 2002-591476	20020516
BG 107477	A	20040130	BG 2003-107477	20030117
US 2004077884	A1	20040422	US 2003-602463	20030623
US 6825362	B2	20041130		
PRIORITY APPLN. INFO.:			IN 2001-CH402	20010518
			WO 2002-IN121	20020516

GI

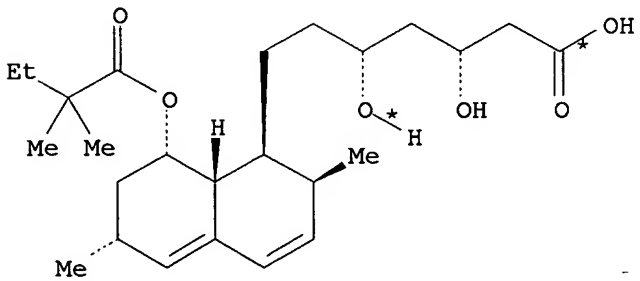
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention discloses a process for preparation of simvastatin (I) from simvastatin acid derivs., such as II [Z = H, NH4], via lactonization. Thus, lactonization of II [Z = NH4], in a mixture of acetonitrile and glacial acetic acid to provide anhydrous conditions at a temperature of 65-70° C afforded I (yield = >97.4%) and a dimer impurity III (<0.1%).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

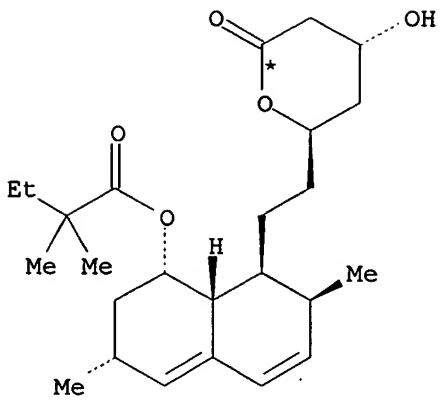
L3 ANSWER 16 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 1 A ===> **B**



● NH_3

A (1) ⟶



B
YIELD 95%

RX(1) RCT A 139893-43-9
RGT C 136108-62-8 Dowex 50X2-400
PRO B **79902-63-9**
SOL 75-05-8 MeCN
NTE ion exchange resin in the acid form, optimization study

ACCESSION NUMBER: 137:232555 CASREACT
TITLE: Preparation of lactone by intramol. esterification and lactonization
INVENTOR(S): Picha, Frantisek; Peters, Theodorus Hendricus Antonius; Lemmens, Jacobus Maria
PATENT ASSIGNEE(S): Synthon B.V., Neth.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072566	A1	20020919	WO 2002-NL161	20020311
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NL 1017548	C2	20020910	NL 2001-1017548	20010309
US 2002147351	A1	20021010	US 2002-94132	20020311
US 6562984	B2	20030513		
EP 1368332	A1	20031210	EP 2002-705606	20020311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NZ 525972	A	20050930	NZ 2002-525972	20020311
ZA 2003003734	A	20040514	ZA 2003-3734	20030514
NO 2003002227	A	20030908	NO 2003-2227	20030516

PRIORITY APPLN. INFO.: NL 2001-1017548 20010309

OTHER SOURCE(S): MARPAT 137:232555
GI

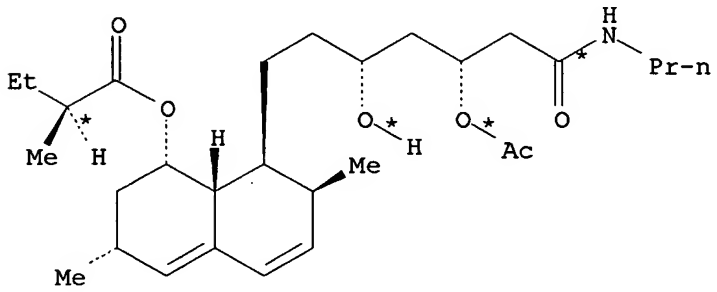
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The synthesis of a compound of formula I comprises in intramol. esterification, lactonization, of a compound of formula II with a lactonization agent in a suitable solvent thus yielding a reaction medium, wherein R is a hydrogen atom or a lower alkyl group, preferably a Me group and X is a hydrogen atom or a cation, wherein the lactonization agent forms a hydrated complex with water, released on the lactonization, which hydrated complex is substantially insol. in the solvent. Thus ammonium salt of simvastatin 2.5 g was reacted in the presence of anhydrous methane sulfonic acid 690 mg to give 1.8 g of simvastatin.

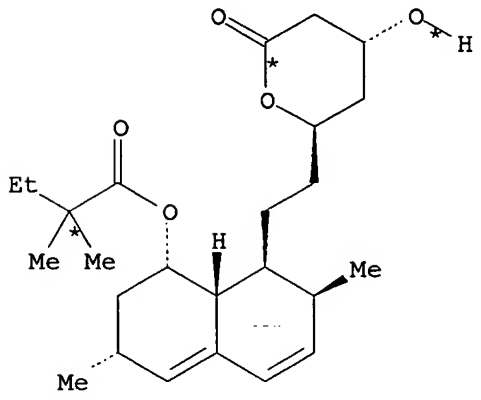
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(3) OF 18 ...H + J ===> **K**



H J



K

RX(3) RCT H 405225-63-0

STAGE(1)
RGT L 123-75-1 Pyrrolidine, M 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RCT J 74-88-4

STAGE(3)
SOL 7732-18-5 Water

STAGE(4)
RGT N 1310-73-2 NaOH
SOL 64-17-5 EtOH, 7732-18-5 Water

STAGE(5)
RGT O 7664-41-7 NH3
SOL 67-56-1 MeOH

STAGE(6)
RGT P 1336-21-6 NH4OH

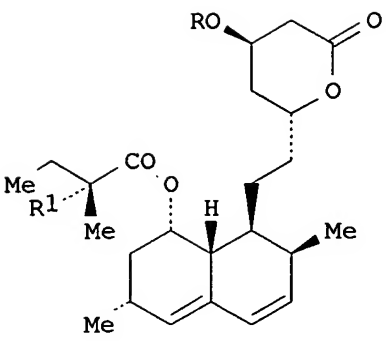
STAGE(7)
SOL 108-88-3 PhMe

PRO K **79902-63-9**
NTE alternative starting materials used

ACCESSION NUMBER: 136:279267 CASREACT
TITLE: Process for manufacturing simvastatin and its novel intermediates starting from lovastatin
INVENTOR(S): Sambasivan, Ganesh
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024675	A1	20020328	WO 2000-IN88	20000913
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001028796	A5	20020402	AU 2001-28796	20000913

PRIORITY APPLN. INFO.: WO 2000-IN88 20000913
OTHER SOURCE(S): MARPAT 136:279267
GI



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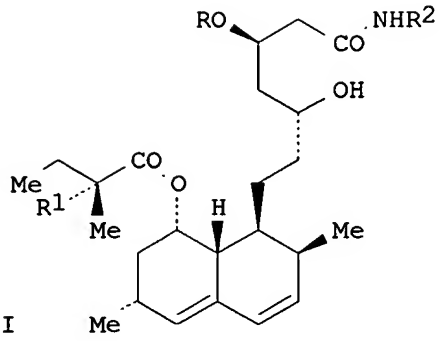


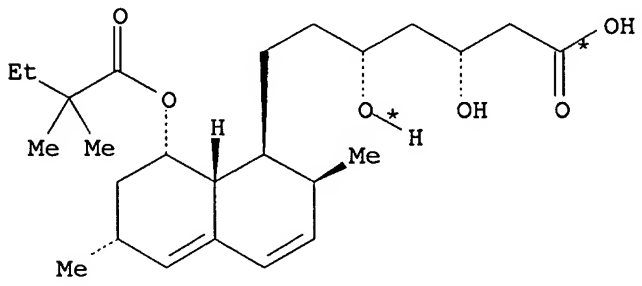
II

AB This invention describes the synthesis of simvastatin from lovastatin by protecting the hydroxy group of the lactone ring and then converting to lovastatin amide using an amine and subsequent reaction with a metal amide base generated from Bu lithium and pyrrolidine and followed by treatment with Me iodide to give desired C-methylated intermediate. This intermediate was further transformed to the final product, simvastatin. This method of production consumes lesser quantities of metal amide, gives fewer side reactions and a lowered overall cost of manufacture of simvastatin than other procedures reported. Thus, lovastatin I (R = R1 = H) was O-silylated with ClSiMe2CMe3 using imidazole in DMF at 50° for 7 h to form I (R = SiMe2CMe3, R1 = H) which the underwent lactone ring opening/amidation in THF at 40° for 12 h with propylamine to form amide II (R = SiMe2CMe3, R1 = H, R2 = propyl) in 90% yield. The amide was then methylated using MeI, BuLi and pyrrolidine in THF to form II (R = SiMe2CMe3, R1 = Me, R2 = propyl) which then underwent a reaction sequence of (1) hydrolysis by refluxing with NaOH in EtOH to form the open-chain acid, (2) ammonium salt formation using 1.5N HCl followed by NH4OH, (3) lactonization by heating the ammonium salt at 100° for 6 h. to give the desired simvastatin I (R = H, R1 = Me).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

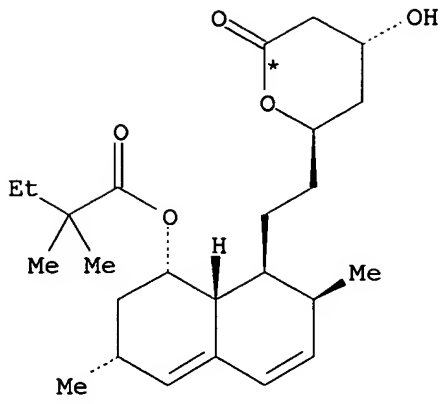
L3 ANSWER 18 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(5) OF 15 ...K ===> **T**



● NH_3

K (5) ⟶



T
YIELD 85%

RX(5) RCT K 139893-43-9

STAGE(1)

STAGE(2)
SOL 108-88-3 PhMe

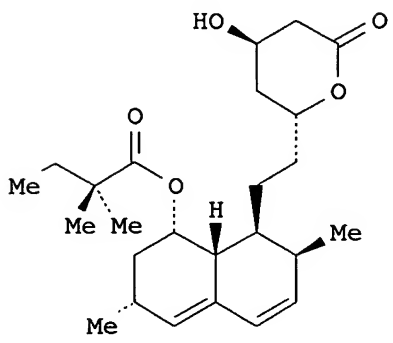
PRO T **79902-63-9**
NTE (100°, 6 h)

ACCESSION NUMBER: 136:167217 CASREACT
TITLE: Highly purified simvastatin compositions
INVENTOR(S): Csaba, Szabo; Ferenc, Korodi; Istvan, Melczer; Szabolcs, Salyi; Leonov, David
PATENT ASSIGNEE(S): Teva Pharmaceuticals Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009697	A1	20020207	WO 2001-US23525	20010726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2419206	AA	20020207	CA 2001-2419206	20010726
US 2002115712	A1	20020822	US 2001-916662	20010726
US 6686481	B2	20040203		
EP 1303268	A1	20030423	EP 2001-961736	20010726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004505045	T2	20040219	JP 2002-515250	20010726
NZ 524418	A	20041224	NZ 2001-524418	20010726

ZA 2003000344 A 20040121 ZA 2003-344 20030113
PRIORITY APPLN. INFO.: US 2000-221112P 20000727
WO 2001-US23525 20010726

GI



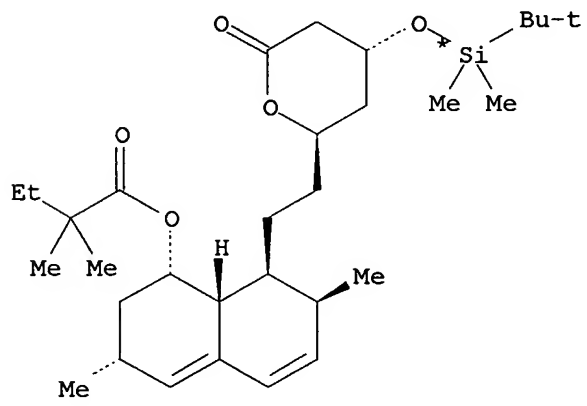
I

AB The present invention relates to a process to prepare semi synthetic statins, to intermediates formed during said process and to highly purified simvastatin (I) produced by the process.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

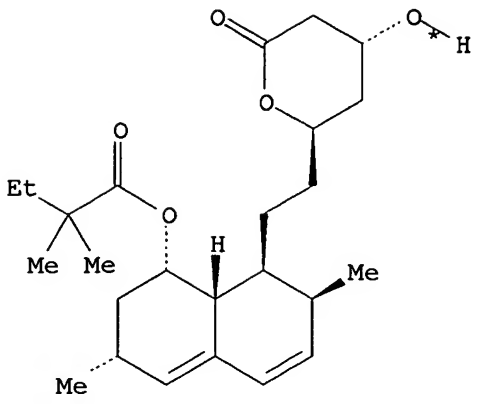
L3 ANSWER 19 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(2) OF 3 ...C ===> **I**



C

(2)



I

RX(2) RCT C 79902-59-3

STAGE(1)
RGT J 75-75-2 MeSO3H
SOL 7732-18-5 Water, 75-05-8 MeCN

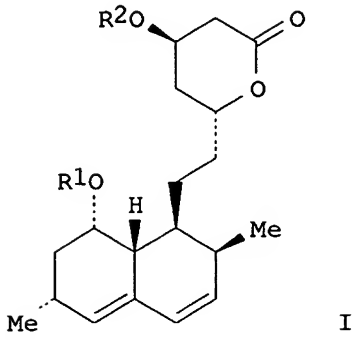
STAGE(2)
RGT K 1310-73-2 NaOH
SOL 7732-18-5 Water

PRO I **79902-63-9**
NTE alternative prepn. shown

ACCESSION NUMBER: 135:272796 CASREACT
TITLE: Process for manufacturing simvastatin
INVENTOR(S): Lee, Kwang Hyuk; Kim, Jin Wan; Choi, Kwang Do; Bae, Hun
PATENT ASSIGNEE(S): Cheil Jedang Corporation, S. Korea
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072734	A1	20011004	WO 2000-KR283	20000330
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000017141	A	20021217	BR 2000-17141	20000330
EP 1268462	A1	20030102	EP 2000-913150	20000330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003528869	T2	20030930	JP 2001-570646	20000330
US 6576775	B1	20030610	US 2002-203633	20020820
PRIORITY APPLN. INFO.:			WO 2000-KR283	20000330

OTHER SOURCE(S): MARPAT 135:272796
GI



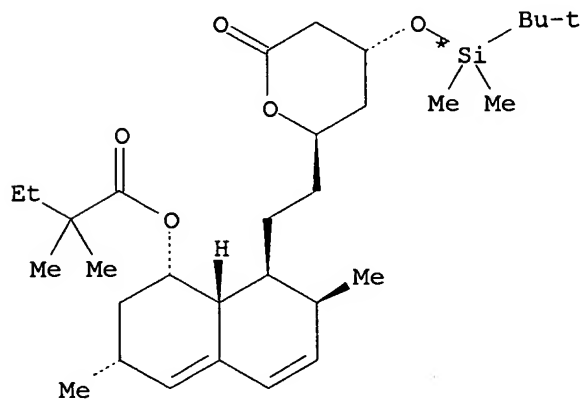
I

AB This invention describes the synthesis of simvastatin I [R1 = COC(Me)2Et; R2 = H (II)] from a substituted tetrahydropyranone I [R1 = H, R2 = TBDMS (III)] via acylation with activated carboxylic acid [IV; Et(Me)2CO2PR3Cl; R = Me, Et, Pr, Bu, t-Bu, Ph]. Thus, 2,2-Dimethylbutyric acid was activated by triphenylphosphine and halogen compds such as hexachloroethane, affording intermediate Et(Me)2CO2P(Ph)3Cl, which was used without separation for esterification of III to give tert-butyldimethylsilyloxy-protected I [R1 = COC(Me)2Et; R2 = TBDMS (V)]. Desilylation of V afforded desired II..

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 15 ...A ===> **B**



A

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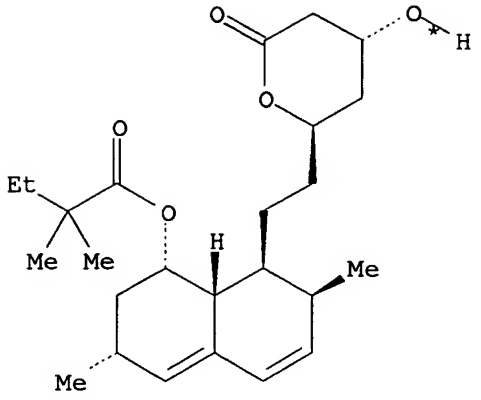


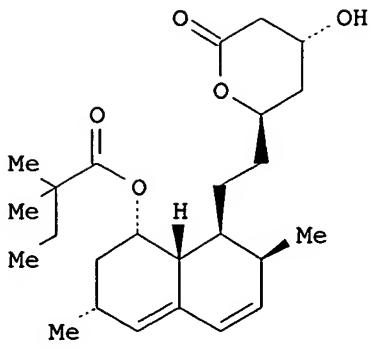
B
YIELD 92%

RX(1) RCT A 79902-59-3
RGT C 7647-01-0 HCl
PRO B **79902-63-9**
SOL 109-99-9 THF, 123-91-1 Dioxane

ACCESSION NUMBER: 135:61179 CASREACT
TITLE: An improved process for preparing simvastatin
INVENTOR(S): Hong, Chung Il; Kim, Jung Woo; Shin, Hee Jong; Kang, Tae Won; Cho, Dong Ock
PATENT ASSIGNEE(S): Chong Kun Dang Pharmaceutical Corp., S. Korea
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045484	A2	20010628	WO 2001-KR301	20010227
WO 2001045484	A3	20020328		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2438477	AA	20010628	CA 2001-2438477	20010227
AU 2001037752	A5	20010703	AU 2001-37752	20010227
JP 2004524260	T2	20040812	JP 2001-546231	20010227
US 2004068123	A1	20040408	US 2003-468852	20030825
US 6833461	B2	20041221		

PRIORITY APPLN. INFO.: WO 2001-KR301 20010227
GI

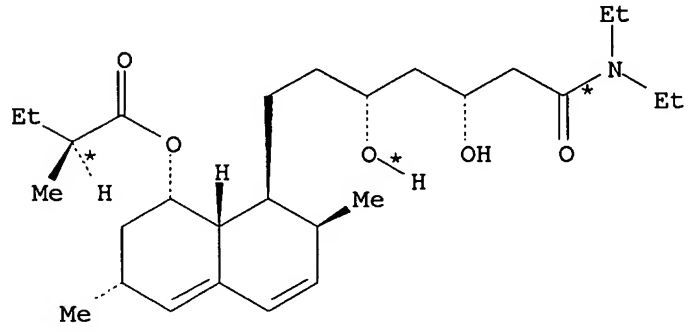


I

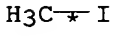
AB Simvastatin (I) was prepared with high yield and high purity by performing the following sequential processes comprising: (i) hydrolysis of lovastatin as starting material with potassium t-butoxide in an organic solvent and small amount of water under a mild reaction condition, followed by lactonization of the obtained solid intermediate with preventing from formation of byproducts; (ii) protection of an alc. group with t-butyldim ethylsilyl group which can be easily removed with concentrated hydrochloric acid without the formation of byproducts; (iii) acylation of the obtained protected intermediate with acyloxytriphenyl phosphonium salt as an acylating agent under a mild reaction condition; and (iv) removal of the silyl protective group with a concentrated hydrochloric acid. The improved process of preparing simvastatin is environmentally sound, economically efficient, and industrially useful.

L3 ANSWER 21 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 5 ...A + B ===> C

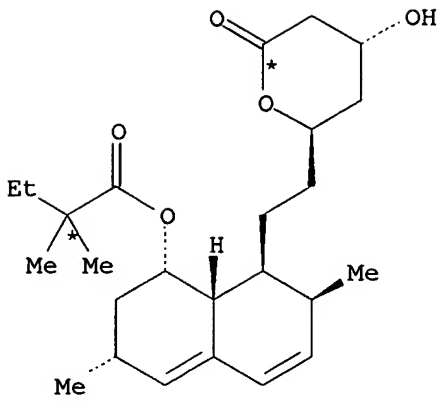


A



B

(1)



C

RX(1) RCT A 339266-09-0

STAGE(1)
RGT D 109-72-8 BuLi, E 123-75-1 Pyrrolidine
SOL 109-99-9 THF

STAGE(2)
RCT B 74-88-4

STAGE(3)
SOL 7732-18-5 Water

STAGE(4)
RGT F 1310-73-2 NaOH
SOL 64-17-5 EtOH, 7732-18-5 Water

PRO C **79902-63-9**
NTE alternative prepns. shown

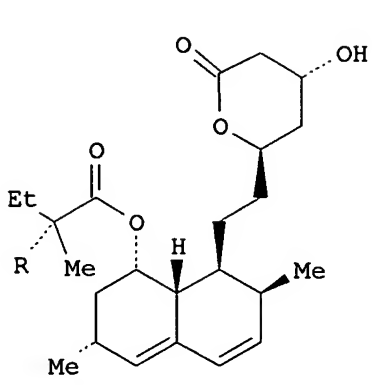
ACCESSION NUMBER: 134:353210 CASREACT
TITLE: Process for manufacturing simvastatin and the novel intermediates
INVENTOR(S): Sambasivam, Ganesh; Sridharan, Madhavan; Acharya, Poornaprajna; Mathew, Joy
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034590	A1	20010517	WO 1999-IN63	19991111

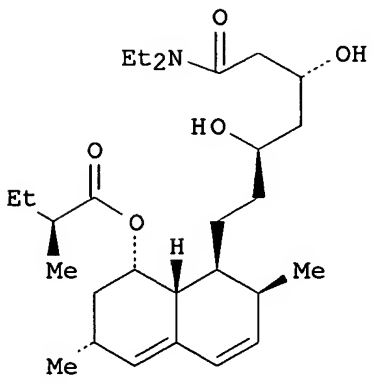
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6573392	B1	20030603	US 2002-129861	20020510
US 6573385	B1	20030603	US 2002-194126	20020712
PRIORITY APPLN. INFO.:			US 1999-129861	19991111
			WO 1999-IN63	19991111

GI



I



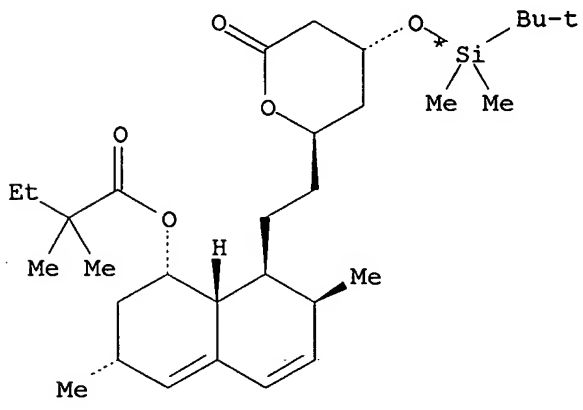
II

AB This invention describes the synthesis of simvastatin (I, R = Me) from lovastatin (I, R = H) by converting lovastatin to the amide using a secondary amine and subsequent reaction with a metal amide base generated from Bu lithium and pyrrolidine and followed by treatment with Me iodide to give desired C-methylated intermediate. This intermediate was further transformed to the final product, simvastatin. This method of production consumes lesser quantities of metal amide, gives fewer side reactions and a lowered overall cost of manufacture of simvastatin than other procedures reported. Thus, lovastatin was treated with Et2N in toluene to give the amide II, which was treated with pyrrolidine, THF and BuLi in THF and then MeI, followed by hydrolysis, cyclization and purification to give simvastatin.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

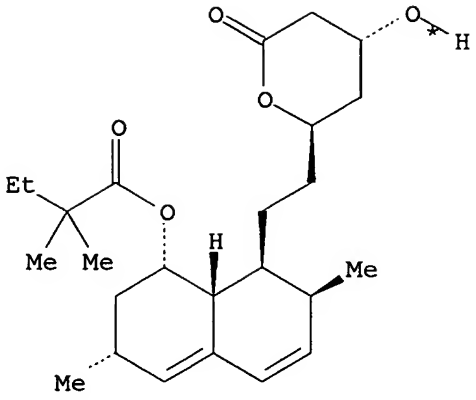
L3 ANSWER 22 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(1) OF 2 A ===> **B**



A

(1) ⟶



B

RX(1) RCT A 79902-59-3

STAGE(1)
SOL 64-19-7 AcOH

STAGE(2)
RGT C 12125-01-8 (NH4)F

PRO B **79902-63-9**
NTE both deprotection conditions and work-up are claimed

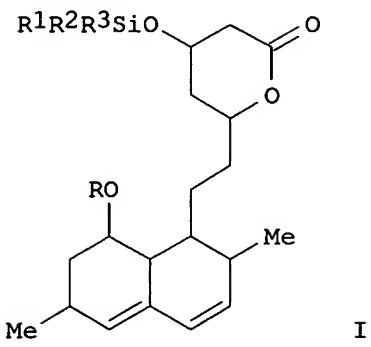
ACCESSION NUMBER: 133:163972 CASREACT
TITLE: Novel process for the removal of a silyloxy protecting group from 4-(silyloxy)tetrahydropyran-2-ones
INVENTOR(S): Zlicar, Marko; Rucman, Rudolf
PATENT ASSIGNEE(S): Lek Pharmaceutical and Chemical Company D.D., Slovenia
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000046217	A1	20000810	WO 2000-IB105	20000202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000021241	A5	20000825	AU 2000-21241	20000202
EP 1149086	A1	20011031	EP 2000-901283	20000202
EP 1149086	B1	20040512		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002536372	T2	20021029	JP 2000-597287	20000202
AT 266653	E	20040515	AT 2000-901283	20000202
ES 2216853	T3	20041101	ES 2000-901283	20000202
US 6509479	B1	20030121	US 2001-869372	20010921

PRIORITY APPLN. INFO.: SI 1999-25 19990204
WO 2000-IB105 20000202

OTHER SOURCE(S): MARPAT 133:163972

GI



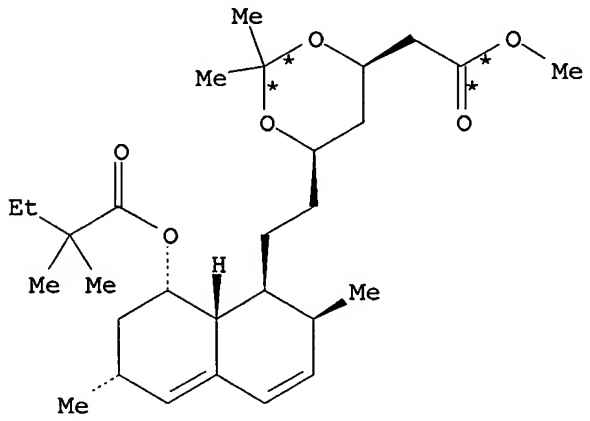
I

AB Silyl protecting groups can be removed from hydroxypyranones such as I (R = acyl; R1, R2, R3 = alkyl, aryl, aralkyl) by treatment with NH4F or (NH4)HF2, and the process is applicable to the preparation of simvastatin and its derivs. and analogs. Thus, 78 g crude tert-butyldimethylsilyloxy simvastatin in 220 mL HOAc was stirred with 40 g NH4F at 45-50° for 4 h, and the mixture was evaporated at 50-60°/3325 Pa to 70 mL, cooled, extracted, washed, evaporated, and dried to give, after recrystn., 35 g simvastatin.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

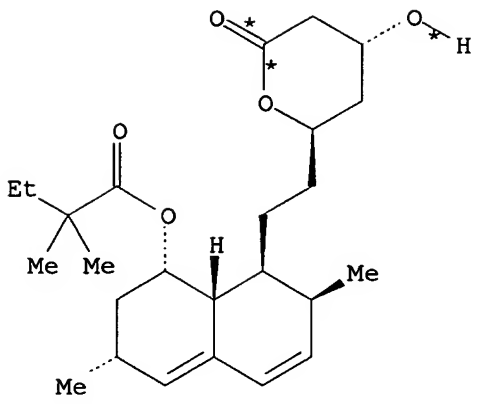
L3 ANSWER 23 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(4) OF 10 ...N ===> Q



N

(4) →



Q

RX(4) RCT N 272456-97-0
RGT R 7647-01-0 HCl
PRO Q **79902-63-9**
SOL 7732-18-5 Water, 75-05-8 MeCN
NTE room temp. for 4 h

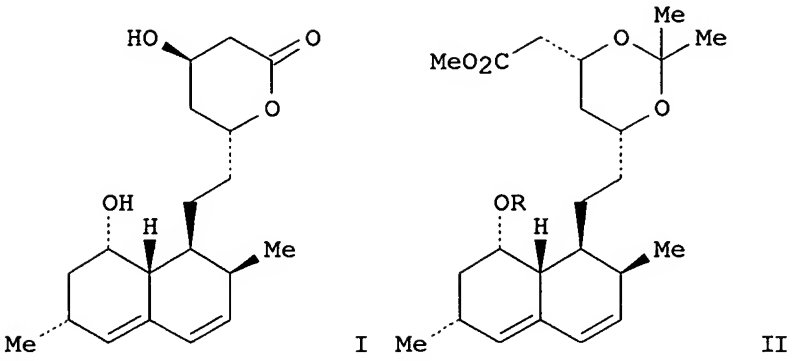
ACCESSION NUMBER: 133:17379 CASREACT
TITLE: Process for producing simvastatin from lovastatin
INVENTOR(S): Taoka, Naoaki; Inoue, Kenji
PATENT ASSIGNEE(S): Kaneka Corporation, Japan
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034264	A1	20000615	WO 1999-JP6929	19991210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320163	AA	20000615	CA 1999-2320163	19991210
EP 1055671	A1	20001129	EP 1999-959738	19991210
EP 1055671	B1	20041201		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
SI 20327	C	20010228	SI 1999-20024	19991210
CN 1122029	B	20030924	CN 1999-802754	19991210
CN 1493570	A	20040505	CN 2003-200315304519991210	
AT 283849	E	20041215	AT 1999-959738	19991210
EP 1533308	A2	20050525	EP 2004-23298	19991210
EP 1533308	A3	20050914		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
ES 2234323	T3	20050616	ES 1999-959738	19991210
US 6331641	B1	20011218	US 2000-601794	20000928

PRIORITY APPLN. INFO.: JP 1998-351865 19981210
EP 1999-959738 19991210
WO 1999-JP6929 19991210

OTHER SOURCE(S): MARPAT 133:17379

GI

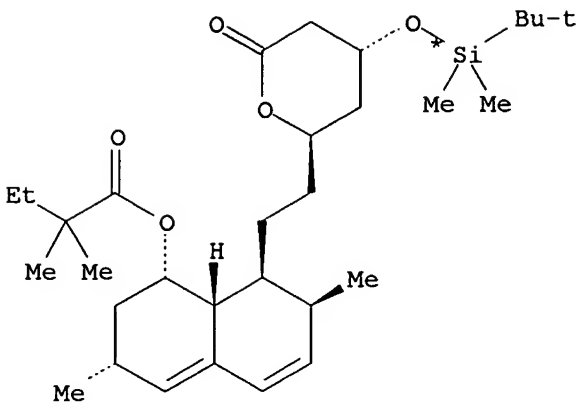


AB A convenient, efficient and industrially favorable process for producing simvastatin, which is useful as an HMG-coA reductase inhibitor (no data), is described. This process comprises deacylating lovastatin by treating with an inorg. base and a secondary or tertiary alc. to thereby form diol lactone, and then selectively protecting, acylating, deblocking, and lactonizing the diol lactone by using a ketal or acetal protective group to thereby give simvastatin. Thus, saponification of lovastatin with KOH in tert-Bu alc. at room temperature for 30 min and then under reflux for 4 h followed by acidification with H3PO4 and treatment with MeSO3H in iso-Pr acetate gave diol lactone (I) which underwent ketalization with 2,2-dimethoxypropane in the presence of p-MeC6H4SO3H in CH2Cl2 at room temperature for 1 h to give acetonide (II; R = H). Acylation of the latter alc. with 2,2-dimethylbutyryl chloride in the presence of 4-dimethylaminopyridine in pyridine at 100° for 6 h gave II (R = MeCH2CMe2CO) which was treated with aqueous 1 N HCl in MeCN at room temperature for 4 h to give simvastatin.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

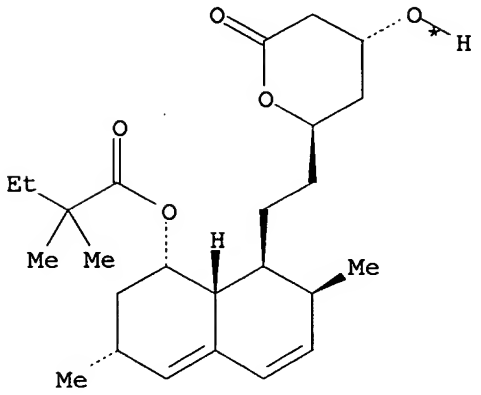
L3 ANSWER 24 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(2) OF 6 ...C ===> **I**



C

(2) →



I
YIELD 77%

RX(2) RCT C 79902-59-3

STAGE(1)
RGT J 75-75-2 MeSO3H
SOL 7732-18-5 Water, 75-05-8 MeCN

STAGE(2)
RGT K 1310-73-2 NaOH
SOL 7732-18-5 Water

STAGE(3)
RGT F 7647-01-0 HCl
SOL 7732-18-5 Water

STAGE(4)
RGT L 1336-21-6 NH4OH
SOL 67-56-1 MeOH

STAGE(5)
SOL 108-88-3 PhMe

STAGE(6)

SOL 110-82-7 Cyclohexane

PRO I **79902-63-9**

ACCESSION NUMBER: 132:22871 CASREACT
TITLE: Preparation of Simvastatin
INVENTOR(S): Yang, Yuh-lin; Liu, Yeuk-chuen
PATENT ASSIGNEE(S): Industrial Technology Research Institute, Taiwan; Yung Shin Pharmaceutical Ind. Co Ltd.
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6002021	A	19991214	US 1998-106278	19980629

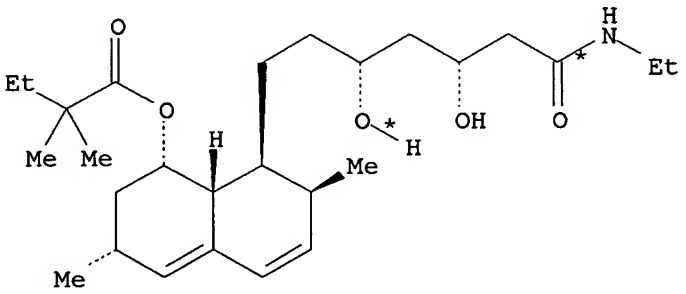
PRIORITY APPLN. INFO.: US 1998-106278 19980629
OTHER SOURCE(S): MARPAT 132:22871

AB Desacyl lovastatin was O-protected and the product treated with EtCMe2COCl in the presence of pyridinium trifluoromethanesulfonate in pyridine/ClCH2CH2Cl to give, after deprotection, simvastatin in 77% total yield (sic).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(5) OF 28 ...N ===> **Q**



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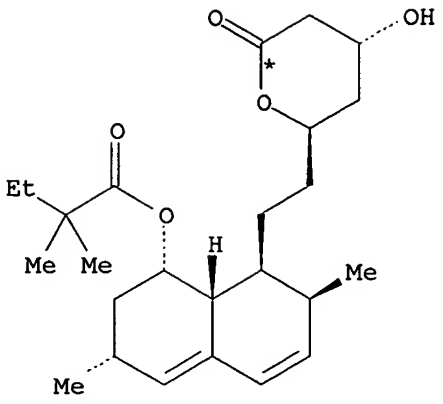
N



Q

RX(5) RCT N 242489-17-4
RGT R 1310-73-2 NaOH
PRO Q **79902-63-9**
SOL 7732-18-5 Water

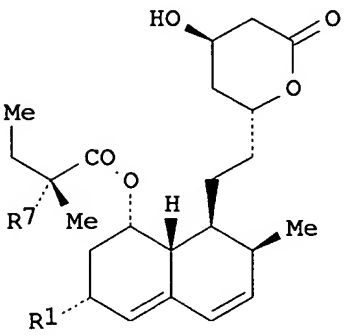
ACCESSION NUMBER: 131:214119 CASREACT
TITLE: Process for producing simvastatin and its derivatives
INVENTOR(S): Van Dalen, Frans; Lemmens, Jacobus Maria; Van Helvoirt, Gertruda Antonetta Philomina; Peters, Theodorus Hendricus Antonius; Picha, Frantisek
PATENT ASSIGNEE(S): Synthon B.V., Neth.
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945003	A1	19990910	WO 1999-NL119	19990305
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 940395	A1	19990908	EP 1998-201762	19980527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 9901045	A	19990906	NO 1999-1045	19990303
CA 2321676	AA	19990910	CA 1999-2321676	19990305
AU 9928612	A1	19990920	AU 1999-28612	19990305
AU 759878	B2	20030501		
CN 1232030	A	19991020	CN 1999-103408	19990305
US 6100407	A	20000808	US 1999-263097	19990305
EP 1064275	A1	20010103	EP 1999-909407	19990305
EP 1064275	B1	20021106		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002505327	T2	20020219	JP 2000-534546	19990305

AT 227280	E	20021115	AT 1999-909407	19990305
ES 2182493	T3	20030301	ES 1999-909407	19990305
PT 1064275	T	20030331	PT 1999-909407	19990305
IL 138119	A1	20040512	IL 1999-138119	19990305
US 6271398	B1	20010807	US 2000-597739	20000619
NO 2000004357	A	20001106	NO 2000-4357	20000901
US 2002035274	A1	20020321	US 2001-882050	20010618
PRIORITY APPLN. INFO.:			NL 1998-1008502	19980305
			EP 1998-201762	19980527
			US 1999-263097	19990305
			WO 1999-NL119	19990305
			US 2000-597739	20000619

OTHER SOURCE(S): MARPAT 131:214119

GI



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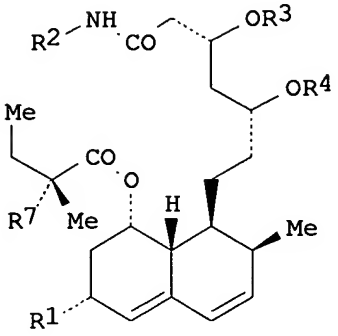


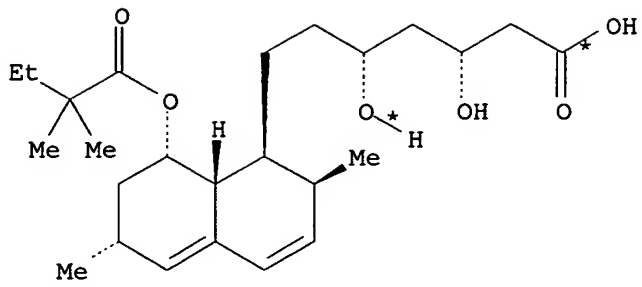
II

AB A process for the preparation simvastatin and its analogs I [R1= H, Me; R7 = Me, Et] via the formation of intermediate amides, such as II [R1= H, Me; R2 = alkyl; R3, R4 = H, hydroxy protecting group, such as THP; R3R4 = diol protecting acetonide, such as CMe2; R7 = H, Me, Et], was described. Thus, (+)-simvastatin I (R1 = R7 = Me) was prepared in a five step synthetic sequence starting from lovastatin and ethanamine via the formation of intermediate amide II [R1 = Me, R2 = Et, R3 = R4 = THP, R7 = H].

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

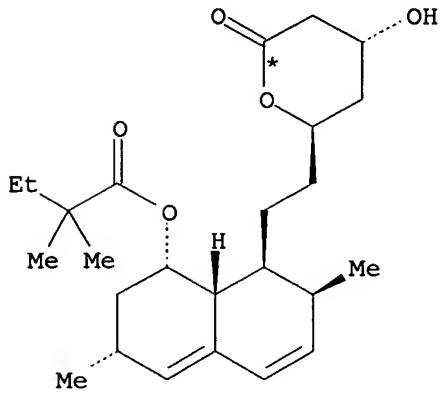
RX(1) OF 2 A ===> **B**



● NH_3

A

(1) ⟶



B
YIELD 91%

RX(1) RCT A 139893-43-9

STAGE(1)
SOL 67-63-0 Me2CHOH

STAGE(2)
CAT 18820-82-1 Pyridine HBr

STAGE(3)
RGT C 7732-18-5 Water

PRO B **79902-63-9**
NTE using pyridine-HCl gave 90% yield

ACCESSION NUMBER: 131:157706 CASREACT
TITLE: Process of lactonization in the preparation of statins
INVENTOR(S): Kumar, Yatendra; Thaper, Rajesh Kumar; Kumar, S. M. Dileep; Khanna, Jag Mohan
PATENT ASSIGNEE(S): Ranbaxy Laboratories Limited, India
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

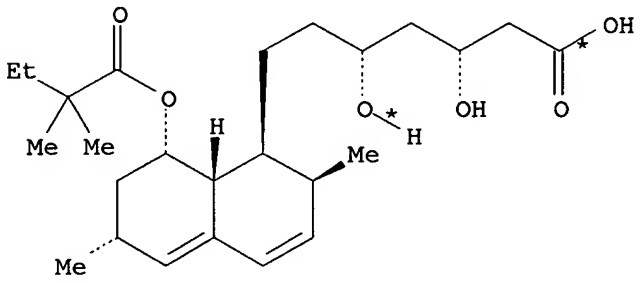
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5939564	A	19990817	US 1998-55572	19980406
PRIORITY APPLN. INFO.:			IN 1997-3101	19971028

AB The title process comprises treating the open ring hydroxy-acid form of the statins or a salt thereof in an organic solvent by heating under anhydrous conditions in the presence of a catalyst comprising a salt of an organic base with an organic or inorg. acid such as pyridine hydrobromide.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

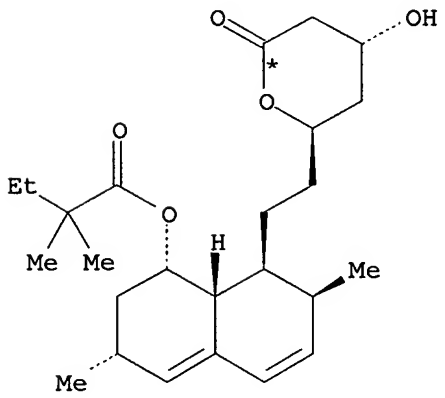
RX(2) OF 2 E ===> **F**



● NH_3

E

(2) →



F
YIELD 98%

RX(2) RCT E 139893-43-9

STAGE(1)

RGT C 64-19-7 AcOH

STAGE(2)
RGT D 7732-18-5 Water

PRO F **79902-63-9**
NTE stereoselective, butylated hydroxytoluene also present, most aspects of process claimed

ACCESSION NUMBER: 131:58747 CASREACT
TITLE: Process of lactonization in the preparation of statins
PATENT ASSIGNEE(S): Ranbaxy Laboratories Limited, India
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5917058	A	19990629	US 1998-64285	19980422
IN 186880	A	20011201	IN 1997-DE3102	19971028
ZA 9810764	A	19990813	ZA 1998-10764	19981125
EP 955297	A1	19991110	EP 1998-123252	19981207
EP 955297	B1	20040421		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 264849	E	20040515	AT 1998-123252	19981207
PT 955297	T	20040831	PT 1998-123252	19981207
ES 2217485	T3	20041101	ES 1998-123252	19981207
RU 2214407	C2	20031020	RU 1998-122366	19981209
HK 1023572	A1	20050225	HK 2000-102749	20000508
PRIORITY APPLN. INFO.:			IN 1997-DE3102	19971028
			US 1998-64285	19980422

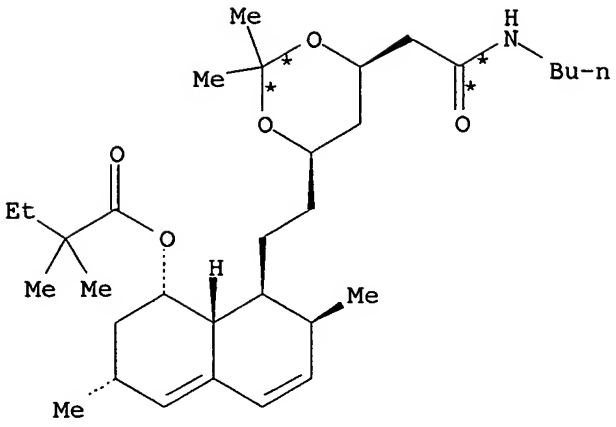
OTHER SOURCE(S): MARPAT 131:58747

AB An improved process of lactonization in the preparation of statins (e.g., the HMG-CoA reductase inhibitors lovastatin and simvastatin) employs very mild reaction conditions. The improved process comprises treating the open ring hydroxy acid form of the statins with an excess of acetic acid and in the absence of a strong acid catalyst under mild heating conditions (e.g., ambient to 55° C.), and adding an anti-solvent to the reaction mixture, thereby causing the statins in lactone form to crystallize from the reaction mixture The acetic acid serves as both a solvent and a catalyst for the lactonization reaction.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

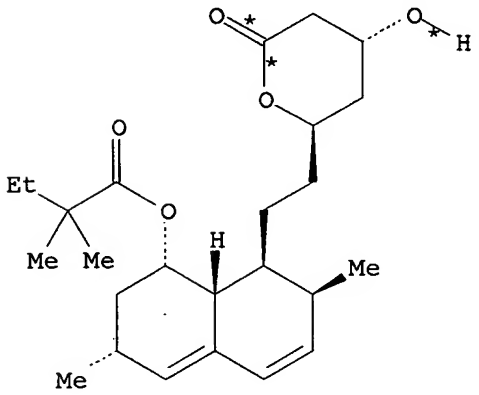
L3 ANSWER 28 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(2) OF 31 ...F ===> **G**



F

(2) →



G

RX(2) RCT F 210980-55-5

STAGE(1)
RGT H 7664-93-9 H2SO4
SOL 108-88-3 PhMe

STAGE(2)
RGT I 1336-21-6 NH4OH

STAGE(3)
RGT H 7664-93-9 H2SO4
SOL 7732-18-5 Water, 108-88-3 PhMe

PRO G **79902-63-9**

ACCESSION NUMBER: 129:161450 CASREACT
TITLE: Process for the production of semisynthetic statins via novel intermediates
INVENTOR(S): Vries, Ton Rene; Wijnberg, Hans; Faber, Wijnand Sjourd; Kalkman-Agayn, Venetka Ivanova; Sibeyn, Mieke
PATENT ASSIGNEE(S): Gist-Brocades B.V., Neth.
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832751	A1	19980730	WO 1998-EP519	19980127
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2278603	AA	19980730	CA 1998-2278603	19980127
AU 9866183	A1	19980818	AU 1998-66183	19980127
AU 747219	B2	20020509		
EP 971913	A1	20000119	EP 1998-908031	19980127
EP 971913	B1	20030416		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 336993	A	20000526	NZ 1998-336993	19980127
JP 2001508782	T2	20010703	JP 1998-531620	19980127
AT 237605	E	20030515	AT 1998-908031	19980127
IL 131044	A1	20030731	IL 1998-131044	19980127
PT 971913	T	20030829	PT 1998-908031	19980127
EP 1340752	A1	20030903	EP 2003-8084	19980127
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ES 2197465	T3	20040101	ES 1998-908031	19980127
IN 188004	A	20020803	IN 1998-DE242	19980128
NO 9903644	A	19990928	NO 1999-3644	19990727
NO 318146	B1	20050207		
US 6294680	B1	20010925	US 2000-341809	20000105
PRIORITY APPLN. INFO.:			EP 1997-200223	19970128
			EP 1997-306809	19970903
			EP 1998-908031	19980127
			WO 1998-EP519	19980127

OTHER SOURCE(S): MARPAT 129:161450
GI

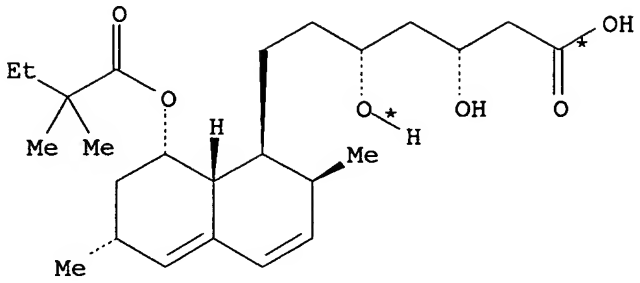
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for the production of semisynthetic statins I [R1, R2 = H, OH, alkyl, aryl, arylalkyl; R3 = H, COR9; R4, R5 = H, alkyl, cycloalkyl, alkenyl, alkynyl, Ph, phenylalkyl; NR4R5 = cyclic amine; R6, R7 = H; R6R7 = BR8, CR10R11, P(O)OR12, SO2; R8 = (un)substituted Ph; R9 = (un)substituted alkyl, cycloalkyl, alkenyl, alkynyl, Ph, phenylalkyl; R10, R11 = H (but not both), (un)substituted alkyl, cycloalkyl, alkenyl, alkynyl, Ph, phenylalkyl; R12 = H, alkyl, cycloalkyl, Ph, phenylalkyl, amine (with R3 = H); dashed lines = single or double bonds] is described. Thus, simvastatin (II) was prepared from lovastatin (III) via ring opening with BuNH2 in PhMe followed by ketalization with acetone containing catalytic p-TsOH; th resulting acetonide is reduced with LiAlH4 in THF; the resulting alc. is acylated with EtCMe2COCl in pyridine containing DMAP followed by heating in aqueous THF containing catalytic p-TsOH and ammoniation with NH4OH in MeOH/EtOH; the resulting ammonium salt is heated to give II.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

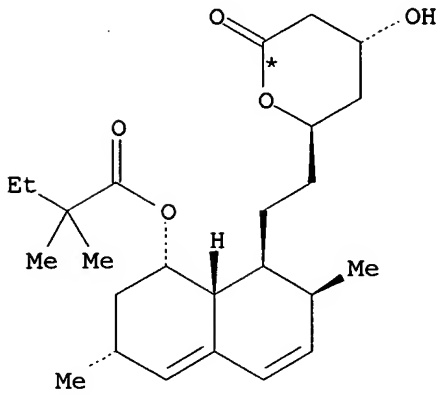
RX(3) OF 14 ...F ===> J



● NH_3

F

(3) →



J

RX(3) RCT F 139893-43-9
PRO J **79902-63-9**
SOL 108-88-3 PhMe

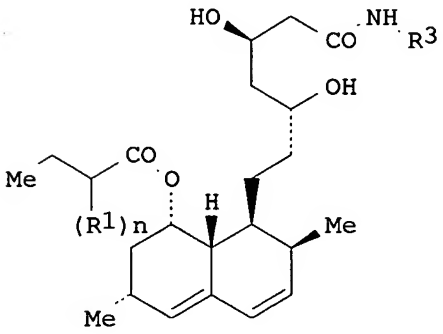
ACCESSION NUMBER: 129:67648 CASREACT
TITLE: Preparation of key intermediates in the manufacture of simvastatin
INVENTOR(S): Khanna, Jag Mohan; Kumar, Yatendra; Thaper, Rajesh Kumar; Misra, Satyananda; Kumar, S. M. Dileep
PATENT ASSIGNEE(S): Ranbaxy Laboratories, Ltd., India
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

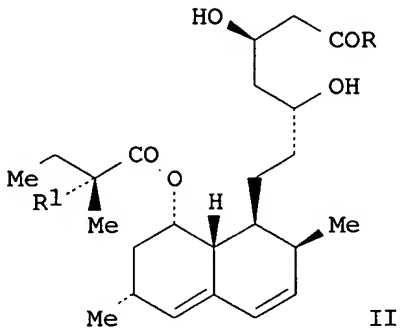
US 5763653	A	19980609	US 1997-816574	19970313
EP 864560	A1	19980916	EP 1997-107059	19970429
EP 864560	B1	20011128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 209627	E	20011215	AT 1997-107059	19970429
ES 2166932	T3	20020501	ES 1997-107059	19970429
AU 692409	B2	19980604	AU 1997-21409	19970514
AU 9721409	A1	19980129		
ZA 9704022	A	19971209	ZA 1997-4022	19970530
CN 1173488	A	19980218	CN 1997-111497	19970530
CN 1101805	B	20030219		
HR 970436	B1	20030630	HR 1997-970436	19970807
CZ 286576	B6	20000517	CZ 1997-2650	19970820
SK 282909	B6	20030109	SK 1997-1165	19970825
PRIORITY APPLN. INFO.:			IN 1996-DE1683	19960530
			US 1997-816574	19970313

OTHER SOURCE(S): MARPAT 129:67648

GI



I



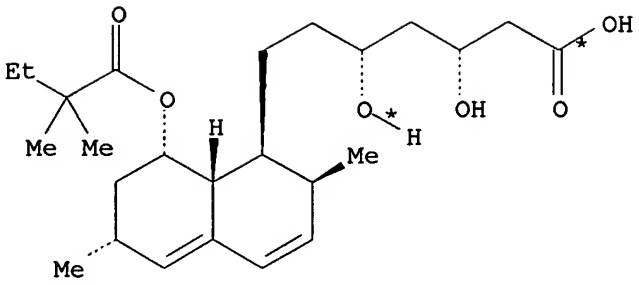
II

AB A process for preparing intermediates I [R1 = Me; R3 = cyclopropyl; n = 1, 2] for preparation of simvastatin from lovastatin or mevinolinic acid salt without protecting and deprotecting the two hydroxy groups of the open pyranone ring was described. Thus, mevinolinic acid ammonium salt was reacted with cyclopropylamine in toluene to form amide II (R = cyclopropylamino, R1 = H) which was then methylated with MeI using lithium pyrrolidide in THF to form amide II (R = cyclopropylamino, R1 = Me). The methylated amide was converted to the ammonium salt II (R = ONH4, R1 = Me) with NaOH and MeOH, which was subsequently transformed to simvastatin by stirring in toluene at 105°. Preparation of simvastatin starting from lovastatin was also presented.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

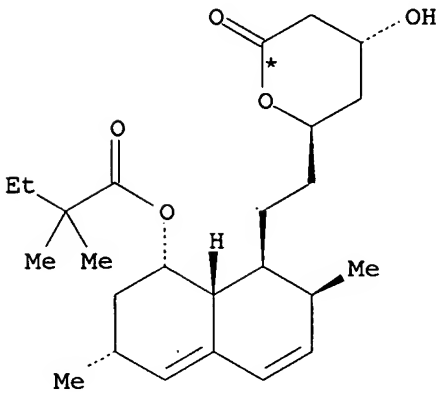
L3 ANSWER 30 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(3) OF 14 ...F ===> J



F

(3) →



J

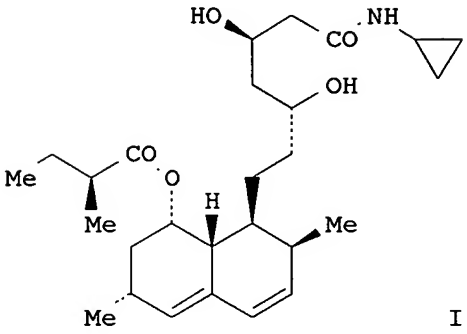
RX(3) RCT F 139893-43-9
PRO J **79902-63-9**
SOL 108-88-3 PhMe

ACCESSION NUMBER: 129:67647 CASREACT
TITLE: Process for manufacturing simvastatin from lovastatin or mevinolinic acid
INVENTOR(S): Kumar, Yatendra; Thaper, Rajesh Kumar; Misra, Satyananda; Kumar, S. M. Dileep; Khanna, Jag Mohan
PATENT ASSIGNEE(S): Ranbaxy Laboratories, Ltd., India
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

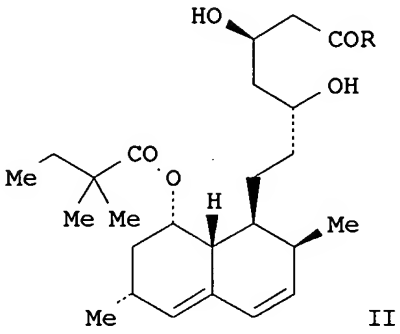
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5763646	A	19980609	US 1997-816573	19970313
ZA 9704023	A	19971210	ZA 1997-4023	19970509
AU 693401	B1	19980625	AU 1997-21408	19970514
CN 1188763	A	19980729	CN 1997-111494	19970530
CN 1102588	B	20030305		

EP 864569	A1	19980916	EP 1997-111277	19970704
EP 864569	B1	20010816		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 204271	E	20010915	AT 1997-111277	19970704
ES 2162165	T3	20011216	ES 1997-111277	19970704
HR 970435	B1	20011231	HR 1997-970435	19970807
TW 427968	B	20010401	TW 1997-86111652	19970814
CZ 290672	B6	20020911	CZ 1997-2649	19970820
SK 283319	B6	20030603	SK 1997-1167	19970825
PRIORITY APPLN. INFO.:			IN 1997-CA175	19970124
			IN 1997-DE175	19970124
			US 1997-816573	19970313

OTHER SOURCE(S): MARPAT 129:67647
GI



I



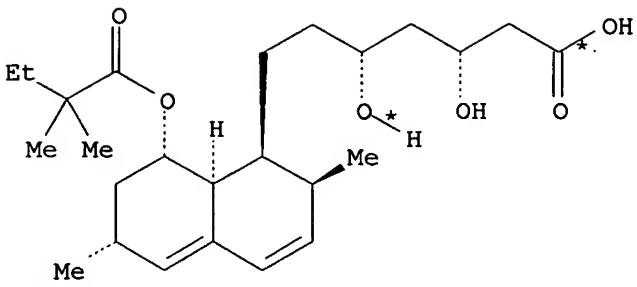
II

AB A process for preparing simvastatin from lovastatin or mevinolinic acid salt without protecting and deprotecting the two hydroxy groups of the open pyranone ring was described. Thus, mevinolinic acid ammonium salt was reacted with cyclopropylamine in toluene to form amide I which was methylated with MeI using lithium pyrrolidide in THF to form amide II (R = cyclopropylamino). The methylated amide was converted to the ammonium salt II (R = ONH4) with NaOH and MeOH, which was subsequently transformed to simvastatin by stirring in toluene at 105°. Preparation of simvastatin starting from lovastatin was also presented.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

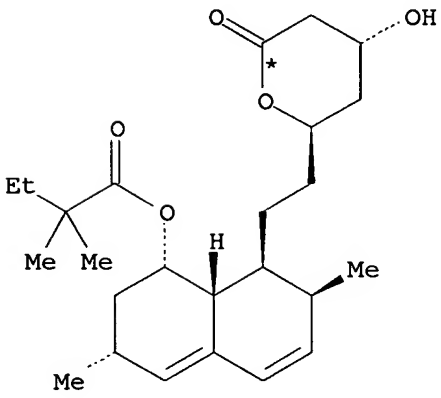
RX(6) OF 21 ...Q ===> **U**



● NH_3

Q

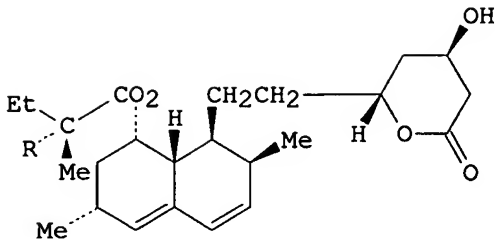
(6) ⟶



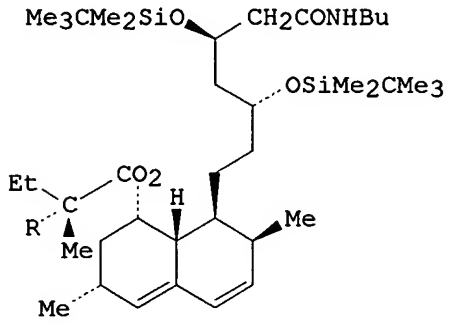
U

RX(6) RCT Q 135093-20-8
PRO U **79902-63-9**
SOL 108-88-3 PhMe

ACCESSION NUMBER: 115:91908 CASREACT
TITLE: Synthesis of synvinolin: extremely high conversion alkylation of an ester enolate
AUTHOR(S): Askin, D.; Verhoeven, T. R.; Liu, T. M. H.; Shinkai, I.
CORPORATE SOURCE: Dep. Process Res., Merck, Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Journal of Organic Chemistry (1991), 56(16), 4929-32
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

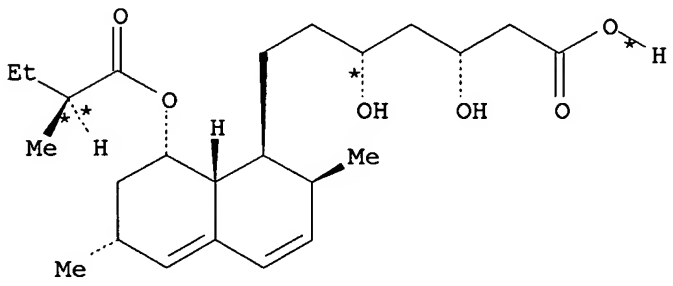


II

AB An efficient process for the com. preparation of the therapeutically important cholesterol lowering drug synvinolin I (R = Me) from mevinolin I (R = H) is reported. The synthesis relies upon deactivation of the δ-lactone carbonyl toward enolization via conversion to the bis(dimethyltert-butylsiloxy) amide II [R = H (III)]. An extremely high conversion (99.7%) ester enolate alkylation of III affords II (R = Me) and its N-Me derivative Subsequent desilylation and intramolecularly assisted basic amide hydrolysis in the presence of the dimethylbutyrate ester moiety followed by lactonization give I (R = Me) in an overall yield of 86% from I (R = H).

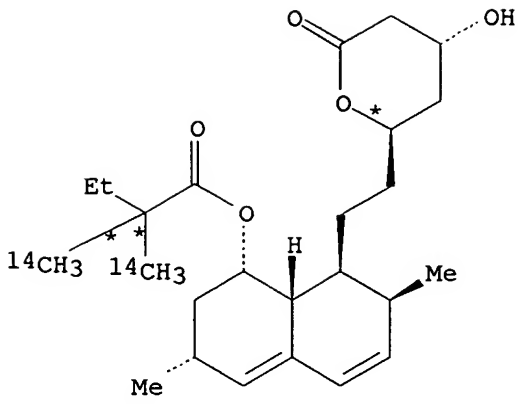
L3 ANSWER 32 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(2) OF 15 ...B ===> **G**...



● K

B (2) →



G

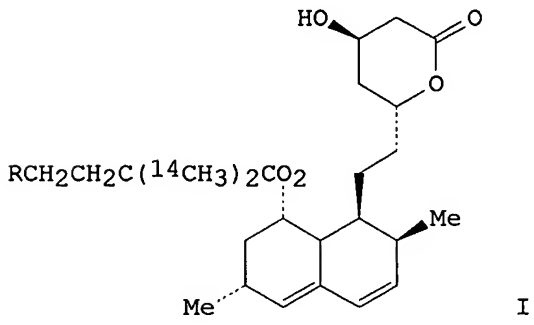
RX(2) RCT B 120664-21-3

STAGE(1)
RGT H 123-75-1 Pyrrolidine, I 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RGT J 16170-82-4 Iodomethane-14C

PRO G **120586-10-9**

ACCESSION NUMBER: 110:212460 CASREACT
TITLE: Carbon-14 methylation of the 2-methylbutyryl side chain of mevinolin and its analogs
AUTHOR(S): Prakash, S. R.; Ellsworth, R. L.
CORPORATE SOURCE: Merck Sharp Dohme Res. Lab., Rahway, NJ, 07065, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1988), 25(8), 815-25
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

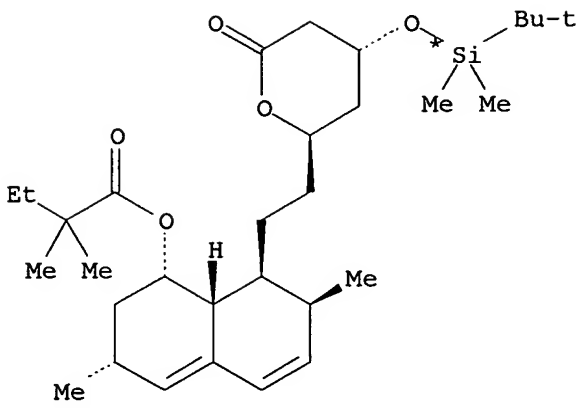


I

AB The mevinolin derivs. I (R = H, OH) and the tetrahydro derivative of I (R = H) were prepared by converting mevinolin and its analogs into the K salts, preparation of the ester enolate, and treatment with 14CH3I, followed by relactonization on chromatog.

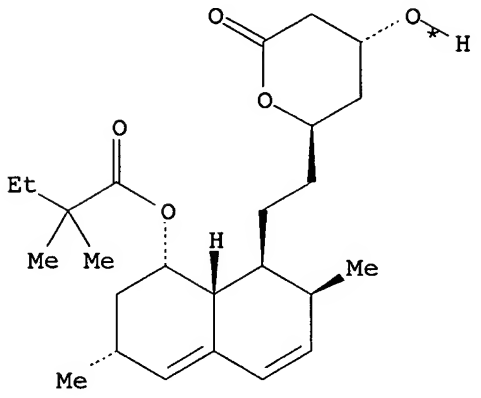
L3 ANSWER 33 OF 33 CASREACT COPYRIGHT 2006 ACS on STN

RX(38) OF 74 ...AT ===> **BO**



AT

(38)



BO

RX(38) RCT AT 79902-59-3
RGT AY 429-41-4 Bu4N.F, AZ 64-19-7 AcOH
PRO BO **79902-63-9**
SOL 109-99-9 THF

ACCESSION NUMBER: 104:186228 CASREACT
TITLE: 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. 4. Side-chain ester derivatives of mevinolin
AUTHOR(S): Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (1986), 29(5), 849-52
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
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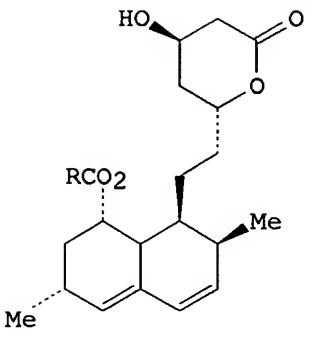
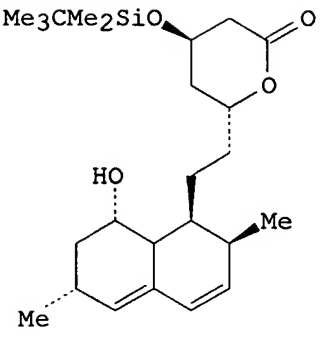


I



II

AB A series of 19 ester analogs (I) of mevinolin was prepared by acylation of the silylated alc. II by 1 of 3 developed procedures, followed by desilylation with Bu4NF-AcOH in THF. A number of the compds. (evaluated as their ring-opened Na salts) showed high anticholesteremic activity (inhibition of rat-liver HMG-CoA reductase), e.g., I (R = Me2CH, CH2:CMeCH2, CF3CHMeCH2).

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=> d his

     (FILE 'HOME' ENTERED AT 09:39:40 ON 16 MAR 2006)

     FILE 'REGISTRY' ENTERED AT 09:39:49 ON 16 MAR 2006
L1              STRUCTURE UPLOADED

     FILE 'CASREACT' ENTERED AT 09:40:37 ON 16 MAR 2006
L2            1 S L1
L3           33 S L1 FULL

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   268.87     269.52

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -23.43     -23.43

STN INTERNATIONAL LOGOFF AT 09:42:46 ON 16 MAR 2006
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